Application of Multivariate Image Analyses in Dementia

Gottlieb, Natalie Nicole

Awarding institution:
King's College London

APPLICATIONS OF MULTIVARIATE IMAGE ANALYSES IN DEMENTIA

Natalie Nicole Gottlieb
Institute of Psychiatry, Psychology & Neuroscience,
King's College London

A thesis submitted in part fulfilment for the degree of Doctor of Philosophy in Neuroimaging

2017

ABSTRACT

The goal of this PhD is to investigate imaging markers of pre-clinical and clinical Alzheimer's disease, mild cognitive impairment, and vascular dementia with a particular focus on the integration of electronic health records. Currently, many of these imaging markers and diagnostic techniques have been validated in research cohorts but not clinical cohorts. This thesis examines the applicability of these tools in a clinical cohort, and aims to validate their accuracy in such a cohort.

To accomplish this I performed four different studies:

Study 1. The integration of electronic health records and automated MRI analysis techniques to determine the relationship between mini mental state exam scores (MMSE) and hippocampal volume, this will also involve the linkage of electronic health records with imaging data which has not been done previously.

Study 2. The application of multivariate image analysis techniques to MRI of dementia patients in clinical practice, to see if current research techniques are applicable to a wider population based cohort.

Study 3. Examining the rate of underdiagnosis of Alzheimer's disease in mixed dementia patients who are clinically diagnosed with vascular dementia, using white matter hyperintensity analysis techniques to ensure those who are diagnosed with vascular dementia are not excluded from helpful treatments currently aimed at Alzheimer's Disease patients only.

Study 4. The creation of a randomised clinical trial of the application of automated hippocampal volumetry measures for dementia patients in clinical practice, with a goal to increase clinical radiologist's confidence when making a diagnosis.

The results of these studies suggest that while the use of these tools in a clinical setting needs more investigation, they hold promise to aid in the diagnosis of dementia.

ACKNOWLEDGMENTS

Firstly, I would like to thank my supervisors, Professor Steve Williams, Dr. Andy Simmons, and Dr. Eric Westman. Without you, your encouragement, and support this thesis wouldn't have been possible. Thank you Eric, for always being available for a skype call with screen sharing to help me figure out analyses. Thank you Andy, for teaching me how to work independently but also supporting me when I needed it most. Thank you Steve, for your enthusiasm in my project, that was always contagious, even when I wasn't so keen myself. You three have made this PhD such a great learning experience, and helped me really foster my love for neuroimaging.

I'd like to also thank Professor Rob Stewart, Dr. Matthew Broadbent, and Megan Pritchard and the entire CRIS team at the BRC Nucleus. Without you, the electronic health record linkages (and this entire thesis) would not be possible. Thank you Megan, for putting up with crazy panicked emails and always being so pleasant to work with!

Thank you Dr. Sergi Costafreda Gonzales for your support with the clinical trial. You helped me navigate through the clinical side of things, and taught me how to run a clinical trial from start to finish.

Thank you to the team at IXICO and Innovate UK for funding this PhD.

And thank you to my wonderful friends. You listened to it all, from tears to complaints to joy filled screams, and words can't tell you how much I appreciate that. I've made such good friends here at King's, and I'm so happy that you were all there from the start. You all never failed to put a smile on my face, even at the worst of times. Thank you to all my friends outside of King's, that I've made here in London – you are all the best anyone could ever ask for! Thank you Kerry Barrett, for always being there for me, even from 5,568 miles away.

Lastly, thank you to my parents. Your unwavering support and encouragement while your daughter flew across the ocean has been nothing short of incredible. I always appreciate the selfies, and pictures of Renee and Lucy and the garden, which if I put them all into a book may actually fill up more pages than this thesis, and it never fails to put a smile on my face.

DECLARATION OF WORK

This thesis presents four studies using memory clinic patients. The studies described in Chapter 3 and Chapter 4 were initially conceived of and designed by Dr. Andy Simmons and Dr. Eric Westman. The Clinical trial described in Chapter 6 was initially conceived of and designed by Dr. Sergi Costafreda Gonzales and Dr. Andy Simmons. The study design of Chapter 5 was designed by myself, Dr. Andy Simmons, and Dr. Eric Westman.

All data used in Chapters 3, 4, and 5 were obtained from the Biomedical Research Centre Memory Clinic Cohort. Electronic Health Record linkages were performed by Dr. Matthew Broadbent and Megan Pritchard. All data used in the clinical trial (Chapter 6) was collected by myself.

Farshad Falahati (Karolinska Institute, Stockholm, Sweden) performed age correction of memory clinic patients in Chapter 4, and all other analyses were my own work.

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

TABLE OF EQUATIONS

LIST OF ABBREVIATIONS

^{11}C-PIB – ^{11}C-Pittsburgh Compound B

^{18}F – Flourine-18

^{1}H-MRS – Proton MRS / Proton Magnetic Resonance Spectroscopy

99mTc-ECD – 99mTechnetium-L,Lethyl cysteinate dimer

99mTc-HMPAO – 99mTechnetium-hexamethyl-propylenamine oxime

ACE – Addenbrooke's Cognitive Examination

AD – Alzheimer's Disease

ADNI – Alzheimer's Disease Neuroimaging Initiative

ADRDA – Alzheimer Disease and Related Disorders

AIREN – Association Internationale pour la Recherche et l'Enseignement en Neurosciences

ANN – Artificial Neural Networks

ANOVA – Analysis of Variance

APOE – Apolipoprotein E

APP – Amyloid Precursor Protein

ASL – Arterial Spin Labelling

AUC – Area Under the Curve

Aβ – β-amyloid

BOLD – Blood Oxygen Level-Dependent

CA – Cornu Ammonis fields

CDR – Clinical Dementia Rating

Cho – Choline

CNS – Centre for Neuroimaging Sciences

CRIS – Clinical Record Interactive Search

CSF – Cerebrospinal Fluid

CT – Computerized Tomography

CV – Cross Validation

CVD – Cerebrovascular Disease

DG – Dentate Gyrus

DLB – Dementia with Lewy Bodies

DMN – Default Mode Network

DSM – Diagnostic and Statistical Manual of Mental Disorders

DT – Decision Trees

DTI – Diffusion Tensor Imaging

DWI – Diffusion Weighted Imaging

EADC-ADNI – European Alzheimer's Disease Consortium and Alzheimer's Disease Neuroimaging Initiative

EEG – Electroencephalography

ERC – Entorhinal Cortex

FDG – ^{18}fluorodeoxy-glucose

FLAIR – Fluid Attenuation Inversion Recovery

fMRI – Functional Magnetic Resonance Imaging

FTLB – Frontotemporal Lobar Dementia

GDS – Geriatric Depression Scale

GM – Grey Matter

GP – General Practitioner

HarP – Harmonized Protocol

HC – Hippocampus

HCS – Healthy Controls

HES – Hospital Episode Statistics

HIPPA – Health Insurance Portability and Accountability Act

ICV – Intracranial Volume

LDA – Linear Discrimination Analysis

LEAP – Learning Embeddings for Atlas Propagation

MCI – Mild Cognitive Impairment

MD – Mixed Dementia

MDT – Multi-disciplinary Team Meeting

mI – myo-inositol

MR – Magnetic Resonance

MRI – Magnetic Resonance Imaging

MRS – Magnetic Resonance Spectroscopy

MTA – Medial Temporal Lobe Atrophy

MTAI – Medial Temporal Atrophy Index

MTL – Medial Temporal Lobe

NAA – N-acetylaspartate

NFT – Neurofibrillary Tangles

NHS – National Health Service

NINCDS – National Institute of Neurological and Communicative Disorders and Stroke

NINDS – National Institute of Neurological Disorders and Stroke

NPI – Neuropsychiatric Inventory

NPV – Negative Predictive Value

ONS – Office for National Statistics

OPLS – Orthogonal Projection to Latent Structures

OSC – Orthogonal Signal Correction

PET – Positron Emission Tomography

PIS – Patient Information Sheet

PIs – Personal Identifiers

PJS – Patient Journey System

PPV – Positive Predictive Value

PRC – Perirhinal Cortex

PRESS – Predicted Residual Sum of Squares

PSEN1 – Presenilins 1

PSEN2 – Presenilins 2

p-TAU – Phosphorylated Tau

rCBF – regional Cerebral Blood Flow

ROC – Receiver Operating Characteristic

ROI – Region of Interest

RSN – Resting State Network

SLaM – South London and Maudsley Hospital

SPECT – Single Photon Emission Computed Tomography

SQL – Structure Query Language

SVM – Support Vector Machines

t-TAU – Total Tau

VaD – Vascular Dementia

VBI – Vascular Brain Injury

VCI – Vascular Cognitive Impairment

VRS – Visual Rating Scales

WM – White Matter

WMH – White Matter Hyperintensities

XML – Extensible Mark-up Language

ypred – Y prediction values (y predicted value)

1 INTRODUCTION TO THE USE OF IMAGING IN DEMENTIA AND INTEGRATION OF ELECTRONIC HEALTH RECORDS FOR RESEARCH PURPOSES

1.1 INTRODUCTION TO DEMENTIA:

1.1.1 Alzheimer's Disease

1.1.1.1 Epidemiology

It is currently estimated that 40 million people worldwide have some form of dementia, and that number is predicted to double every 20 years until 2050 (Prince et al., 2013). This figure mainly includes those aged older than 60 years, with only less than 1 per 4000 cases under the age of 50 years. AD is the most common form of dementia, with an estimated 60-70% of dementia cases attributed to the disease (Jindal, Bhatt, Sk, & Singh Malik, 2014; Philip Scheltens et al., 2016).

Approximately only 10% of AD patients are diagnosed as early-onset (younger than age 65) (Cacace, Sleegers, & Van Broeckhoven, 2016; Vieira et al., 2013). Unlike late-onset dementia, which is regarded as a complex disease with varied etiology, early-onset AD is almost entirely genetically determined. It has been proposed the heritability of the disease ranges between 92% and 100% (Wingo, Lah, Levey, & Cutler, 2012). Research has found that mutations in three main genes, amyloid precursor protein (APP) and presenilins 1 and 2 (PSEN1 and PSEN2) are part of the autosomal dominant causes of early-onset AD (Cacace et al., 2016). Approximately 10% of early-onset cases are due to autosomal dominant gene mutations, while the other cases are due to autosomal-recessive causes (Wingo et al., 2012).

Late-onset dementia is a much more complicated disease, with an etiology that remains relatively unclear. When looking at the genetics of late-onset dementia, it is clear the Apolipoprotein E (APOE) gene has the greatest influence on disease development. Those with the APOE4 variant of the gene have

a lifetime risk for AD greater than 50%. Those with one APOE4 variant and one APOE3 variant have a 20-30% lifetime risk, compared for 11% for men and 14% for women regardless of APOE genotype (Genin et al., 2011), meaning there is a dose-dependent effect of genotype (Corder et al., 1993).

1.1.1.2 Neuropathology

AD is a gradual, irreversible, neurodegenerative disease characterised by extracellular β-amyloid (Aβ) plaques, neurofibrillary tangles (NFT), and subsequent systematic atrophy throughout the brain (Braak & Braak, 1991; Hampel, Frank, et al., 2010). Typical clinical manifestation is presented as memory impairment and executive dysfunction severe enough to impede daily activities (G. McKhann et al., 1984; Philip Scheltens et al., 2016). Other times, patients can exhibit uncommon manifestations such as language, visual, executive problems before, and more distinctly, than memory deficits (Alladi et al., 2007; Philip Scheltens et al., 2016). These presentations with prominent cognitive impairment in other domains besides memory, like prominent apraxia, language problems or executive dysfunction may occur and are more common in early-onset AD (Koedam et al., 2010; Mendez, 2017). Early-onset AD also has greater neocortical pathology, particularly in the parietal cortex, greater tau compared with amyloid burden, and less hippocampal atrophy (Mendez, 2017).

1.1.2 Current diagnostic criteria of Alzheimer's Disease

According to the National Institute of Neurological Disorders and Stroke (NINCDS) and Alzheimer Disease and Related Disorders (ADRDA), histological evidence from post mortem examination is the only way to prove the underlying pathology and root of the clinical symptoms is actually AD, and therefore give a diagnosis of definite AD (Dubois et al., 2007; G. McKhann et al., 1984). However, disease onset is decades before death and between 10 and 15 years before symptom manifestation (Sperling et al., 2011), once significant brain changes have already occurred. In order to treat patients, and research for cures and interventions, much earlier diagnoses are needed. Because of this, and the occasionally lack of

consistent neuropathology, there is doubt that the current 'gold standard' of post mortem confirmation is actually useful (Philip Scheltens & Rockwood, 2011).

The original criteria for the clinical diagnosis of AD was first established by the NINCDS and ADRDA in 1984 (G. McKhann et al., 1984). These guidelines have since been revised to incorporate the advances in the scientific community that now allow us to visualise more of the pathophysiological processes occurring in AD and the new conceptualizations of the clinical spectrum of AD that includes Mild Cognitive Impairment (MCI) and the preclinical stages of the disease (Albert et al., 2011; Jack Jr. et al., 2011; G. M. McKhann et al., 2011; Sperling et al., 2011). The original model did not account for cognitive impairment that did not meet the threshold for an AD diagnosis, and did not recognize the slow development of AD pathology over time. Additionally, one of the most important observations since the original criteria is that the pathology of AD is not always consistent with the presentation of the disease. In some cases, neuropathology such as Aβ plaques can be present in the absence of any cognitive impairment (Knopman et al., 2003), while others can exhibit unconventional symptomology (Alladi et al., 2007).

Clinical diagnosis must include a detailed history from the patient and their carers, neuropsychological testing, and analysis of the progression of symptoms (G. M. McKhann et al., 2011; Philip Scheltens et al., 2016). The core clinical criteria for diagnosis provides adequate diagnostic accuracy in a majority of patients (G. M. McKhann et al., 2011).

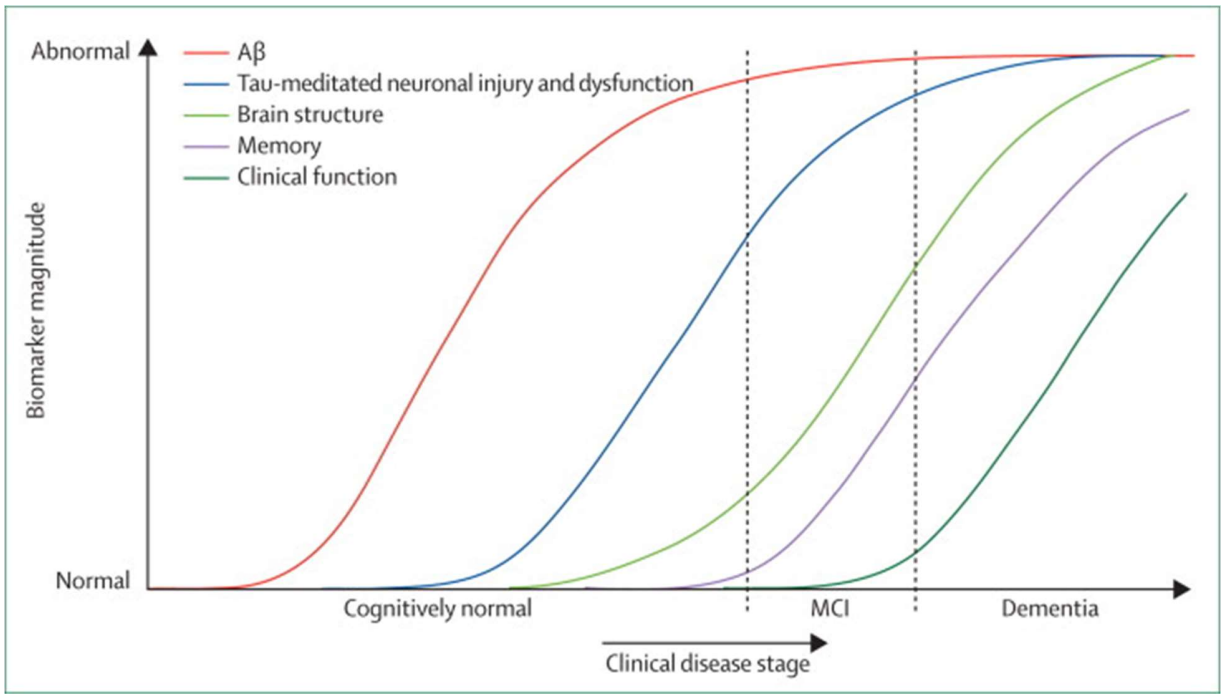
These new guidelines take use of biomarkers into consideration, and their ability to detect pathology in the absence of the traditional AD symptomology.

1.1.2.1 The Preclinical Stage of Alzheimer's Disease

Perhaps one of the most important changes to the diagnostic criteria has been the identification of a prodromal/preclinical AD stage. Those diagnosed as preclinical AD are defined as having evidence of AD

pathology based on any number of biomarkers, in the absence of any cognitive decline or other AD symptomology (Dubois, Hampel, et al., 2016). This distinction is essential for progression of AD research, and it estimated that early interventions delaying clinical onset by one year could reduce the prevalence of AD by 9 million cases by 2050 (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007). One of the greatest challenges in defining preclinical AD is there is yet to be a definite profile of AD pathology that leads to the development of AD in the future. A specific combination of biomarkers that are mostly likely to predict AD would aid in selecting appropriate populations for clinical trials and pre-clinical therapeutic intervention. Additionally, current therapeutic interventions that have not been successful may be more likely to be effective if applied earlier in the disease time course (Sperling et al., 2011). A working hypothetical model of the biomarkers observed in AD has been proposed, but the model is not universal to all preclinical AD patients (Figure 1-1) (Jack Jr et al., 2010).

Figure 1-1 – Dynamic biomarkers of the Alzheimer's pathological cascade. Aβ is identified by CSF Aβ42 or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment. From Jack et al. 2010 (Jack Jr et al., 2010).



1.2 Biomarkers in Alzheimer's Disease and Dementia

Biological markers, or biomarkers, are biological characteristics that can be measured objectively and used as an indicator normal or pathological processes in the body (Biomarkers Definitions Working Group., 2001). A biomarker can be any substance, structure, or process that can be measured within the body or its products, and can predict the incidence or outcome of a given disease or disorder (World Health Organization & International Programme on Chemical Safety, 2001). Ideally, a biomarker is reproducible, widely available and directly reflects disease processes (Biomarkers Definitions Working Group., 2001).

Biomarkers can be categorised by their use, including diagnostic biomarkers, staging/prognostic biomarkers, and biomarkers used to monitor clinical response to medical or therapeutic interventions. Diagnostic biomarkers are used to identify those with a disease or abnormal condition, whereas staging/prognostic biomarkers determine disease stage and severity, and can predict further cognitive decline or improvement. Lastly, biomarkers can be used to measure biological responses to an intervention, making them useful in clinical trial settings (Biomarkers Definitions Working Group., 2001).

In dementia specifically, biomarkers can be used to distinguish aspects of underlying pathology, predict cognitive decline and conversion between disease states (such as MCI to AD), and monitor response to treatment (Ahmed et al., 2014). When looking at AD, biomarkers can further be broken down into the pathologies the reflect.

1.2.1 Biomarkers of Alzheimer's Disease Pathology

There are two groups of well validated biomarkers currently used in AD research and diagnostics, ones that measure Aβ accumulation and ones that measure neuronal degeneration or injury, which can be measured by tau proteins (Jack Jr. et al., 2011). However, AD is characterized as a disease with an extremely complex etiology, and there are many other biochemical processes at play. Oxidative stress

and inflammation markers may give insight to a variety of pathways that are disrupted in AD, and could provide additional information on AD pathology. They are yet to be well-validated, and are not currently used in research cohorts or as a diagnostic tool and therefore will not be discussed here (Albert et al., 2011).

Recently, a new classification system, the "A/T/N" system, has been proposed by Jack and colleagues (Clifford R. Jack et al., 2016). Here, seven major AD biomarkers (further described in detail in subsequent sections) are divided into three categories: "A" or Aβ biomarkers (such as CSF Aβ-42 or Aβ Positron Emission Tomography (PET) imaging), "T" or Tau biomarkers (such as CSF phosphorylated tau or Tau PET imaging), and "N" or biomarkers of neurodegeneration and neuronal injury (such as [^{18}F]-fluorodeoxyglucose PET, structural MRI, or CSF total tau).

This new system allows for a more comprehensive view of AD pathology, and potentially insight into the temporal order of development in patients. Additionally, it provides the opportunity to identify patients that may not have a typical presentation of AD.

1.2.1.1 Aβ deposition

Accumulation of abnormally folded Aβ in systematic distribution in the brain is a hallmark of AD (Braak & Braak, 1991). There is strong genetic, pathological, and biochemical evidence that abnormalities in the production of and removal of Aβ in the brain leads to this aggregation of misfolded proteins, creating plaques (Villemagne & Chételat, 2016). This was originally thought to be the primary event in the cascade that leads to further neurofibrillary degradation, widespread atrophy and ultimately dementia (Karran, Mercken, & Strooper, 2011; Masters, Cappai, Barnham, & Villemagne, 2006). However, more recent studies suggest that this may very well occur in parallel to other pathological events but may not be sufficient on its own to cause AD (Chételat, 2013; Pimplikar, Nixon, Robakis, Shen, & Tsai, 2010). Numerous studies have found Aβ in cognitively normal individuals, suggesting these individuals may go

on to develop symptoms later on. Undoubtedly, Aβ plaques play an important role in AD and abnormalities with Aβ may become apparent in patients 10-20 years before any kind of symptom onset (Jack Jr. et al., 2011). Because of this large lag in symptom onset, Aβ biomarkers are essential in defining at-risk/preclinical AD patients.

1.2.1.2 Neuronal injury

The secondary hallmark of AD as described by Braak and Braak are neurofibrillary changes in the brain (Braak & Braak, 1991). Similarly to Aβ plaques, NFT contain aggregates of hyperphosphorylated tau proteins and are distributed in a systematic way throughout the brain (Kaj Blennow, de Leon, & Zetterberg, 2006). In addition to tau markers, AD causes a wide variety of larger scale functional and structural changes within the brain which are also assumed to reflect wide-scale neuronal damage and dysfunction. These include volume loss in the hippocampus and medial temporal lobe as measured by automated volumetry techniques or visual inspection, global brain atrophy, and reduced metabolism or perfusion (Albert et al., 2011).

1.2.2 Cerebrospinal fluid Biomarkers

Cerebrospinal fluid (CSF) analysis allows for measurement of concentrations of both Aβ and tau. The characteristic CSF profile for AD patients is low Aβ-42 and high total tau (t-tau) and phosphorylated tau (p-tau) (Hampel, Blennow, et al., 2010). In the context of CSF, t-tau is a marker of the intensity of neurodegeneration, while p-tau is indicative of neurofibrillary pathology specifically (Philip Scheltens et al., 2016). Core CSF biomarker measurements appear to have high diagnostic accuracy (Kaj Blennow et al., 2007; de Leon et al., 2007; Hansson et al., 2007; Mattsson et al., 2009, 2011) and high sensitivity and specificity of 85-90% when trying to identify prodromal AD in the MCI stage (Shaw et al., 2009; Pieter Jelle Visser et al., 2009). CSF markers are important in clinical diagnostic decision making because of their negative predictive value; normal levels of all three markers almost completely excludes AD (Philip

Scheltens et al., 2016). Unfortunately, the variability of cut-off points, and lack of standardisation in methods used to collect and analyse CSF samples hinders the ability to create normative data for balanced use and interpretation in clinical practice (Ahmed et al., 2014; Hort, Bartos, Pirttilä, & Scheltens, 2010).

1.2.2.1 Cerebrospinal Fluid Biomarkers of Aβ-42

The aggregates of Aβ in the brain that are a result of dysfunction in the production and clearance of the Aβ protein are reflected in measures of Aβ-42 in CSF. This is because slower Aβ removal from the brain is likely to lead to Aβ deposition and therefore lower CSF concentrations (Bateman et al., 2006; Mawuenyega et al., 2010). On average, Aβ-42 concentrations are reduced to approximately 50% of control concentrations (Kaj Blennow et al., 2006). Studies have found correlations between Aβ-42 in CSF and amyloid plaque load both ante-mortem (Tapiola et al., 2009) and post-mortem (Strozyk, Blennow, White, & Launer, 2003), signifying that CSF Aβ-42 measures are indicative of brain pathology.

1.2.2.2 Cerebrospinal Fluid Biomarkers of Tau Proteins

Because t-tau is an indicator of overall neurodegeneration and neuronal injury, reflecting the size of tissue damage, it is not specific to AD (Hesse et al., 2001; Ost et al., 2006). In AD CSF t-tau levels increase approximately 300% from control concentrations (Kaj Blennow et al., 2006). Studies have found t-tau levels to be associated with rapid decline from MCI to AD (Blom et al., 2009), and potentially indicative of quicker cognitive decline and a high mortality rate in AD patients (Sämgård et al., 2010; Wallin, Hansson, Blennow, Londos, & Minthon, 2009), indicating they are an important biomarker for AD diagnosis.

Conversely, p-tau appears to be more indicative of AD as it reflects both the phosphorylation of tau and formation of neurofibrillary tangles within neurons (Kaj Blennow, Hampel, Weiner, & Zetterberg, 2010). Unlike t-tau that is exhibited in numerous neurodegenerative disease, other brain damage, and healthy

ageing, p-tau is more specific to AD (K. Blennow et al., 1995; Sjögren et al., 2001). Studies that have obtained CSF samples during life and at autopsy have found that p-tau levels correlate well with neurofibrillary tangles and rate of hippocampal atrophy (Buerger et al., 2006; Hampel et al., 2005; Tapiola et al., 2009). Furthermore, tau phosphorylated at a specific binding site (p-tau 181) is linked with faster progression to AD from MCI (Blom et al., 2009) and particularly swift decline once AD is diagnosed (Sämgård et al., 2010). p-tau is also capable of distinguishing AD from other forms of dementia, such as dementia with Lewy bodies (DLB) (Hampel et al., 2004), making it very important for differential diagnoses in the clinic.

1.2.3 Neuroimaging Biomarkers in Alzheimer's Disease and Dementia

Imaging is often used to rule out other brain abnormalities when making a diagnosis of dementia (R. Duara et al., 2008; G. M. McKhann et al., 2011), but there is also use in diagnosing MCI or identifying the preclinical stage of AD (Albert et al., 2011; Sperling et al., 2011). Aside from ruling out non-neurodegenerative conditions, imaging is used to measure the extent and pattern of brain atrophy (Barkhof, 2011). Brain atrophy is a neuropathological feature of dementia, and shows similar patterns in most patients with AD and MCI (Braak & Braak, 1991). These patterns can inform clinicians and researchers about type of dementia (in addition to AD, such as vascular dementia (VaD), frontotemporal lobar dementia (FTLB), DLB, dementia associated with Parkinson's and other movement disorders, and alcohol induced dementia) and stage of dementia (Barkhof, 2011; Qizilbash et al., 2002). Brain imaging techniques, measuring both structural and functional changes, can help make a diagnosis in a timelier manner, allowing patients to receive the care they need earlier on. Right now, unstructured reporting by a radiologist is the most common method of image analysis used in clinics, however some clinics do use structured rating scales (L.-O. Wahlund et al., 2016). The most frequently used structural imaging techniques are computed tomography (CT) and Magnetic Resonance Imaging (MRI). While MRI does show better soft tissue contrast, CT is also used in a clinical setting due to cost, or reasons that prevent

the patient from being eligible for an MRI scan such as a pacemaker or claustrophobia (Barkhof, 2011). MRI is most often the preferred method of structural imaging, and is often the best for visualisation of vascular changes that may indicate VaD (Harper, Barkhof, Scheltens, Schott, & Fox, 2014; Philip Scheltens et al., 2016). If structural imaging does not provide additional information about disease progression, functional imaging may give insights to changes in brain activity that are indicative of changes in neuronal health and furthermore dementia.

1.2.3.1 Structural Imaging Biomarkers – Magnetic Resonance Imaging and Computerised Tomography

The majority of patients with AD or MCI show a standard pattern of atrophy throughout the medial temporal lobe (MTL), specifically in the entorhinal cortex (ERC) and hippocampus (HC) (Braak & Braak, 1991). These patterns of atrophy are associated with the declarative memory deficits that are part of the core clinical criteria of AD and MCI (McDonald et al., 2012; Sarazin et al., 2010). This is measured using structural imaging techniques such as MRI and CT. Currently, while hippocampal and MTL atrophy are observed in a majority of AD and MCI patients, it is not sufficient to diagnose the disease on its own (G. M. McKhann et al., 2011; Schröder & Pantel, 2016). This is due partially because of the methodological differences in atrophy measurements, but also because of the pathological susceptibilities of the hippocampal tissues from other disorders outside of AD (Schröder & Pantel, 2016). Lastly, because of the heterogeneity of AD, there is a variety of presentations in patients and not all experience hippocampal atrophy to the same extent (Daniel Ferreira, Verhagen, et al., 2017).

1.2.3.1.1 Visual Rating scales

Visual rating scales (VRS) are one of the most commonly used tools to support dementia diagnosis. Based on several studies, VRS are a reliable tool for deciding degree of atrophy (Hyun Cho, Kwon, & Seo, 2009; Philip Scheltens, Launer, Barkhof, Weinstein, & van Gool, 1995; Urs et al., 2009; L. O. Wahlund et

al., 2001; L.-O. Wahlund, Julin, Johansson, & Scheltens, 2000; L.-O. Wahlund, Junlin, Lindqvist, & Scheltens, 1999; Westman, Cavallin, Muehlboeck, et al., 2011b).

Scheltens and colleagues created a well-known MTL scale that uses coronal MRI or CT images. Scheltens rating scale gives a medial temporal lobe atrophy (MTA) score of 0-4 based on width of the choroid fissure, width of the temporal horn, and height of the HC (Ph Scheltens et al., 1992). This method has been shown to accurately predict progression from MCI to dementia in subjects diagnosed with prodromal AD (Charles DeCarli et al., 2007).More scales have been created based on Scheltens scale, providing reliable measures of individual MTA structures such as the HC, ERC, and perirhinal cortex (PRC) (R. Duara et al., 2008; Urs et al., 2009; Wattjes et al., 2009).

One problem with the MTA scale is that it is not specific to AD. MTA occurs in a number of other types of dementia as well, especially FTLD (Barkhof, 2011). To address this, Galton et al. proposed a more specific rating scale that focuses on more detailed scoring of the temporal pole and lateral temporal lobe (Galton et al., 2001). While MTA is a characteristic finding in those with amnesic type presentations, especially AD patients with the APOE4 allele (Pereira et al., 2014a), it may be milder in those who are presenile, non-amnestic typed dementia patients.

The Global Cortical Atrophy Scale (GCA) is used to visually assess cortical atrophy, taking into consideration not only degree of atrophy but also degree of lobar and regional atrophy (Pasquier et al., 1996; L.-O. Wahlund et al., 2016). This is also vital for patients with atypical AD with atrophy that is focused in the frontal and posterior areas, instead of the temporal areas normally seen in AD (Daniel Ferreira, Verhagen, et al., 2017).

The posterior/parietal atrophy rating scale looks at three different planes for right and left brain separately. If there are multiple scores on different orientations, the highest score is used. These scores focus on the posterior cingulate, precuneus, and superior parietal regions (Barkhof, 2011; Koedam et al.,

2011; Lehmann et al., 2012). While not as popular as the GCA, it may also be useful in younger patients with atypical AD.

In addition to atrophy, a variety of VRS are also used to assess white matter changes associated with ageing and dementia. They are mainly designed to be used with MRI or CT scans, however some can be used with both. A simple, commonly used scale is the Fazekas scale (Fazekas, Chawluk, Alavi, Hurtig, & Zimmerman, 1987), which gives a score from zero to three. Other scales are more complicated, such as the Age-Related White Matter Changes scale (L. O. Wahlund et al., 2001), the Scheltens White Matter Changes scale (Philip Scheltens et al., 1998), and Manolio's scale which scores based on a template (Barkhof, 2011; Manolio et al., 1994).

It is important to note that atrophy is also a function of normal ageing (Barkhof, 2011), and therefore normal scores on a VRS are affected by age (Barkhof, 2011; R. M. Duara et al., 2013; Pereira et al., 2014a). VRS are subject to individual rater variation, which may introduce some biases into each evaluation. Another limitation of some of the VRS is they are based on assessments of a single slice, which limits the perspective of the entire brain pathology.

1.2.3.1.2 Manual and Automated Volumetric Biomarkers

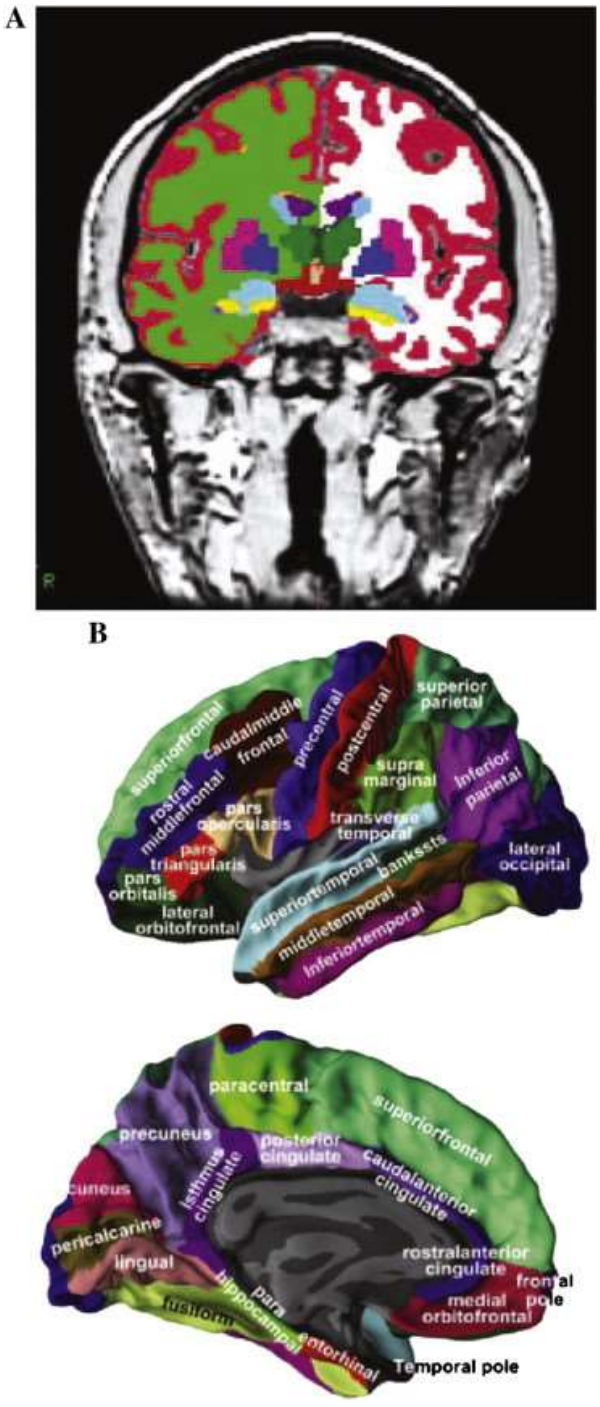
Quantitative imaging techniques often give a more detailed assessment, and wider perspective, than a VRS. There are a variety of quantitative methods that can give substantial information about changes in the brain, provided both the image type and image quality are suitable for the desired technique (Barkhof, 2011).

Hippocampal volume is the most frequently measured variable aside from whole brain volume in patients with AD, and it has been found to have substantial predictive accuracy of diagnosis of the disease without any other additional variables (Barkhof, 2011; Westman, Simmons, Zhang, et al., 2011). A common approach to region of interest (ROI) analysis is manual outlining by a human. While this is a

frequently used approach, it can be variable. It is important to have clear anatomical boundaries and using high resolution T1 weighted images, with voxel sizes around 1x1x1 mm^3, can provide such boundaries. Manual hippocampal delineation also depends on the exact protocol used and software utilised to do the segmentation, in addition to individual rater variation (Barkhof, 2011). The European Alzheimer's Disease Consortium and Alzheimer's Disease Neuroimaging Initiative (EADC-ADNI) Harmonized Protocol (HarP) is one of the largest initiatives to standardise manual hippocampal delineation protocols. The initiative surveyed a variety of manual segmentation protocols, finalised selected landmarks and agreed on a suitable language for segmentation directions (Boccardi et al., 2011; Duchesne et al., 2015). The HarP has demonstrated significantly increased agreement amongst raters (G. B. Frisoni et al., 2015). Even with the high validity, one of the biggest disadvantages to manual segmentation is the time consuming nature, which makes it impractical for clinical use (Westman, Simmons, Zhang, et al., 2011).

A second option for ROI analysis is an automated method done with segmentation software, such as FREESURFER (Figure 1-2) (Bruce Fischl, 2012) or LEAP (Wolz et al., 2010). These outline brain regions and calculate individual volumes, but often significantly depend on image quality. Additionally, they often require large amounts of computing power and some human interaction.

Figure 1-2 - *Representations of Regions of Interest (ROIs) as segmented in FREESURFER. (A) Regional subcortical volumes. (B) Regional cortical thickness measures. From Westman et. al 2012 (Westman, Muehlboeck, & Simmons, 2012).*



Segmentation based analysis aim to distinguish grey matter (GM), white matter (WM) and CSF voxels in the brain based on their image intensity, and location in a given space such as a template. Voxels are

assigned an intensity describing the probability it belongs in each group (GM, WM, or CSF) (Barkhof, 2011).

Registration based and deformation based analysis are used to determine the rate of cerebral atrophy in a patient over time, by aligning scans taken at two separate time points. Registration based methods do not need a large amount of computing power, and deformation based method are only moderately more computing intensive, both need to have comparable scan acquisitions (scanner, coil, pulse sequence) (Barkhof, 2011).

In addition to the quantitative methods looking at brain atrophy, there are also new methods to quantify measures of white matter changes assessed by visual rating scales as well. These techniques use automated detection methods and vary from semi-automated programs to fully automated (Damangir et al., 2012; Gibson, Gao, Black, & Lobaugh, 2010; Iorio et al., 2013; Samaille et al., 2012; Smart, Firbank, & O'Brien, 2011; van der Lijn et al., 2012).

1.2.3.1.3 Hippocampal Subfield Measurements

Because hippocampal volume is one of the most well-studied biomarkers of AD and dementia, it makes sense to look more carefully at the details of this structure. The advances in MRI technology in the past decade have made it possible to visualise the subfields of the HC in vivo. In the past, the HC was looked at as a single entity, and its volume as a whole has been used to evaluate AD. However the HC is a heterogeneous structure, with various subfields containing different connectivity to the rest of the brain and different cellular structure. These subfields have been divided by the cytoarchitectonics of the hippocampus to include several cornu ammonis fields (CA1–CA4), the dentate gyrus (DG), and the subiculum (Aggleton, 2012; de Flores, La Joie, & Chételat, 2015). It is presumed these various sub regions serve different functions, and therefore experience varied vulnerability to disease and injury (de Flores et al., 2015; Small, Schobel, Buxton, Witter, & Barnes, 2011). While the advent of higher

resolution MRI allows us to better visualize anatomical landmarks to delineate subfields, it is still not possible to view the cytoarchitectonics at the cellular level, and therefore subfield segmentation is still an approximation.

Specifically in AD, neuropathology develops at different paces in various sub regions of the HC. The HC is one of the primary targets of AD pathology as first described by Braak and Braak, most specifically the NFTs and subsequent neuronal loss (Braak & Braak, 1991). According to a variety of studies, NFTs first appear in CA1, followed by CA2, CA3, and finally CA4 and the DG (Braak & Braak, 1991; Braak, Braak, & Bohl, 1993; Fukutani et al., 2000; Lace et al., 2009; Schönheit, Zarski, & Ohm, 2004). Following this, neuronal loss occurs mostly in CA1 as demonstrated in histological samples (West, Coleman, Flood, & Troncoso, 1994), and seems to correlate with disease severity (J. L. Price et al., 2001).

While there are clear advantages of examining the HC at the subfield level, this also poses many difficulties. Firstly, there is a lack of standardisation of both manual and automated subfield measurement, with differences across number of segmented subfields, which subfields are grouped together, actual subfield borders, and if segmentation is performed on the entire HC or just a portion of it (de Flores et al., 2015; Maruszak & Thuret, 2014). This lack of standardisation makes it difficult to implement these techniques in clinical practice. Additionally, subfields are usually only able to be segmented at high field strengths (minimally 3T and up) which are not often available clinically. As a result, hippocampal subfield segmentation shows significant promise in research but cannot be posed as a useful clinical biomarker at the current time.

1.2.3.2 Molecular Imaging Biomarkers in Alzheimer's Disease and Dementia

1.2.3.2.1 FDG Positron Emission Tomography

Glucose is integral to healthy cell function in the brain, and general brain health can be assessed by measuring the metabolism of glucose in the brain. This is most commonly done by using Positron

Emission Tomography (PET), and numerous studies have found changes in metabolic brain metabolism in AD using ^{18}fluorodeoxy-glucose (FDG) (Cohen & Klunk, 2014; Karl Herholz, 2012; Johnson, Fox, Sperling, & Klunk, 2012). In AD, this is most commonly manifested as decreased consumption of the FDG in the temporoparietal and posterior cingulate cortices (Coleman, 2005; Devanand et al., 1997; Jagust, Reed, Mungas, Ellis, & Decarli, 2007; Salmon et al., 1994), which reflects neuronal metabolism and therefore neuronal health. Patients with MCI exhibit similar patterns of hypometabolism (Chetelat et al., 2003; Chételat et al., 2005; Lisa Mosconi et al., 2006), as do cognitively healthy individuals with some form of one of the early-onset gene mutations (Kennedy et al., 1995; Rossor, Kennedy, & Frackowiak, 1996). Hypometabolism as demonstrated by FDG-PET has shown to be correlated with cognitive function (Furst et al., 2012; Landau et al., 2011) and may be predictive of further decline (Drzezga et al., 2003, 2005; L. Mosconi et al., 2004). Longitudinal measures of FDG-PET have shown a similar continuous decline in brain metabolism (Alexander, Chen, Pietrini, Rapoport, & Reiman, 2002; Karl Herholz, 2012; Hirono, Hashimoto, Ishii, Kazui, & Mori, 2004), further supporting the notion that is directly related to cognitive function.

FDG-PET is also particularly helpful in drug development and clinical trials for AD, as it can measure pharmacological effects within a few weeks in smaller sample sizes (K. Herholz, Boecker, Nemeth, & Dunn, 2013).

Unfortunately, FDG-PET's high cost and current lack of regulatory approval and standardisation make it a suboptimal biomarker.

1.2.3.2.2 Aβ PET ligands

In addition to measuring Aβ decrease in CSF, Aβ deposition in the brain can be measured in-vivo using PET imaging. The first Aβ PET imaging study was conducted well over a decade ago (Klunk et al., 2004), and since a number of tracers have been developed to measure Aβ deposition in the brain. These

tracers bind to the amyloid proteins in the brain with high affinity. Quantitative and visual assessments of the patterns of ligand distribution in the brain closely represent the pattern of Aβ deposition found in the brain at autopsy, which includes Aβ deposition beginning in the orbitofrontal and inferior temporal cortices and cingulate gyrus, and later spreading to the remaining prefrontal, lateral temporal, and parietal cortices (Braak et al., 1993; Villemagne & Chételat, 2016). The most successfully tracer, and for some time the most widely used, is ^{11}C-Pittsburgh Compound B (^{11}C-PIB) (Villemagne et al., 2017). There is about 80% agreement between (^{11}C-PIB) and CSF measures when classifying a patient as Aβ positive or negative (Villemagne & Chételat, 2016). As expected, PET studies have shown a vast difference in Aβ retention in AD patients and healthy age-matched controls using both ^{11}C-PIB (Furst et al., 2012; Clifford R. Jack, Lowe, et al., 2008; Klunk et al., 2004; John C. Morris et al., 2009; J. C. Price et al., 2005; C. C. Rowe et al., 2007; Christopher C. Rowe et al., 2010) and other radiotracers (Barthel et al., 2011; Camus et al., 2012; Cselényi et al., 2012; Fleisher et al., 2011; Kudo et al., 2007; Villemagne et al., 2011). The pattern of Aβ deposition as visualised by PET imaging follows what is found at autopsy (Braak & Braak, 1991). As previously mentioned, Aβ accumulation can occur 10-20 years before symptom onset and is apparent in Aβ PET imaging (De Meyer et al., 2010; Mintun et al., 2006; Pike et al., 2007; Christopher C. Rowe et al., 2010; Sojkova et al., 2011). As many as 25-35% of non-demented individuals over 60 years of age present with ^{11}C-PIB positive scans, despite performing normally on cognitive tests (Mintun et al., 2006; C. C. Rowe et al., 2007; Christopher C. Rowe et al., 2010). This figure fits with the findings that approximately 25% of non-demented adults over the age of 75 have Aβ deposition in the brain post-mortem (Davies et al., 1988; Forman et al., 2007; J. C. Morris & Price, 2001). Additionally, the frequency of high retention ^{11}C-PIB patients increases each decade as the same rate as the prevalence of non-demented subjects with Aβ plaques at autopsy (Christopher C. Rowe et al., 2010).

Unfortunately, the 20 minute decay half-life of the tracer limits use and makes it too costly for routine clinical use. Several second generation Aβ tracers have been created using fluorine-18 (^{18}F), which has a

half-life of 110 minutes, making it more practical for use in both clinics and research. These include ^{18}F-florbetapir (Clark et al., 2011; Wong et al., 2010), ^{18}F-florbetaben (Barthel et al., 2011; Christopher C. Rowe et al., 2008; Villemagne et al., 2011), ^{18}F-flutemetamol (Nelissen et al., 2009; Vandenberghe et al., 2010), and ^{18}F-NAV4694 (Cselényi et al., 2012), all of which to seem to compare well with ^{11}C-PIB studies showing marked differences between AD patients and age-matched controls in the relevant brain areas (Barthel et al., 2011; Camus et al., 2012; Cselényi et al., 2012; Fleisher et al., 2011; Furst et al., 2012; Clifford R. Jack, Lowe, et al., 2008; Klunk et al., 2004; Mintun et al., 2006; John C. Morris et al., 2009; Pike et al., 2007; J. C. Price et al., 2005; Rabinovici et al., 2007; C. C. Rowe et al., 2007; Christopher C. Rowe et al., 2010; Villemagne et al., 2011, 2017).

1.2.3.2.3 TAU PET Ligands

Similarly to Aβ, ligands have recently been developed to measure tau distribution in the brain in-vivo (Bischof, Endepols, van Eimeren, & Drzezga, 2017). This has been much more challenging as tau aggregates are usually found intraneuronally, and tau aggregates are not found as abundantly as Aβ plaques. There are varying forms of tau pathology in the brain, including straight filaments and paired helical filaments (Bischof et al., 2017), and different ligands may bind to one or both of these types of tau. There has been evidence that these tau PET ligands display tracer retention patterns that mirror the expected tau-pathology in AD (Chien et al., 2013; Hanna Cho et al., 2016; Johnson et al., 2016; Schöll et al., 2016; Schwarz et al., 2016). However, current tau PET tracers are not comprehensively validated, and need to be explored further before being used in a clinical setting.

1.2.3.3 Single Photon Emission Computed Tomography

Another popular functional imaging technique that measures brain activation is perfusion Single Photon Emission Computed Tomography (SPECT). Similarly to PET, perfusion SPECT uses gamma-emitting isotopes to measure regional cerebral blood flow (rCBF). There is a correlation between CBF, neuronal

activity, and metabolism known as neurovascular coupling. This correlation allows deductions to be made about brain activity without direct measurement (Vestergaard et al., 2016). Because of the characteristic pattern of hypometabolism in temporoparietal areas of the brain in AD, SPECT can be a useful technique in the differential diagnosis of the disease (Weih et al., 2010). Studies have shown SPECT has decent histological correlation in an number of patients at autopsy (Bonte, Weiner, Bigio, & White, 1997). SPECT is most often used to rule out AD rather than confirm it, as the sensitivity of SPECT lags far behind the sensitivity. The two most popular ligands used in SPECT perfusion are 99mTechnetium-hexamethyl-propylenamine oxime (99mTc-HMPAO) and 99mTechnetium-L,Lethyl cysteinate dimer (99mTc-ECD) (Dougall, Bruggink, & Ebmeier, 2004).

1.2.3.4 Other Imaging Methods in Alzheimer's Disease and Dementia

The above list of imaging biomarkers used in dementia and AD is by no means and exhaustive one. There are a multitude of other techniques including Functional Magnetic Resonance Imaging (fMRI), Arterial Spin Labelling (ASL), Diffusion Tensor Imaging (DTI) and Magnetic Resonance Spectroscopy (MRS). However these are less validated and not often, if ever, used in the clinic. More research is required to learn if these techniques are useful in a clinical setting.

1.2.3.4.1 Functional Magnetic Resonance Imaging

Aside from looking at brain activation using PET and SPECT imaging, researchers have studied the impact of dementia on the functional connectivity of the brain using fMRI. fMRI is based on the blood oxygen level-dependent (BOLD) signals. The magnetic susceptibility differs between oxygenated and deoxygenated blood, because of the varying levels of iron. Brain activation of a certain area will result in the brain sending more oxygenated blood to that area, resulting in an increase of BOLD signal. This intrinsic contrast allows for the measurement of brain function without the use of radioactive tracers, like those used in PET imaging.

Functional brain connectivity can be measured in two ways: spontaneously at rest and during a task. Spontaneous fluctuations in brain activity at rest can be measured using resting-state fMRI. Brain regions that are temporally correlated, or coactivated with similar timecourses, especially in low-frequency fluctuations less than 0.1 Hz are defined as resting-state networks (RSNs) and represent inherent organisation of functional brain networks (Biswal, Van Kylen, & Hyde, 1997; Damoiseaux et al., 2006). Previous studies have shown decreased functional connectivity throughout the brain at rest in patients with AD and MCI compared to controls (Allen et al., 2007; He et al., 2007; Yong Liu et al., 2008; Wang et al., 2006; Zhang et al., 2010), namely in the default mode network (DMN) (Celone et al., 2006; Greicius, Srivastava, Reiss, & Menon, 2004; Rombouts et al., 2009). The DMN includes the anterior and posterior cingulate, the lateral parietal and prefrontal areas, inferior and middle temporal gyri, cerebellar areas, and extends into the MTL (Damoiseaux et al., 2006; Filippini et al., 2009; Raichle et al., 2001; S. M. Smith et al., 2009). The RSN is of particular interest because many of these areas are heavily involved in AD, and are some of the first areas to be affected by the disease (Mintun et al., 2006; Sheline et al., 2010). It is especially interesting that the pattern of Aβ deposition closely mirrors the DMN (Buckner et al., 2005; Sperling et al., 2009; Villemagne & Chételat, 2016). Additionally, studies have found that connectivity is negatively correlated with disease severity, supporting the theory of a connection between the two (Wu et al., 2011; Zhang et al., 2010).

In addition to measuring the brain at rest, fMRI can be used to measure brain activation in response to specific stimuli or tasks. This can be particularly useful when looking at the effects of AD on episodic memory and related problematic areas. Reduction in episodic memory is a function of natural ageing, and is heavily affected in a variety of dementias making it a prime target for AD studies (Nyberg, 2017). Studies looking at memory in AD patients have shown altered activation in the MTL and parietal lobes, which is consistent with deficits seen in structural scans (Hampel, Frank, et al., 2010). Furthermore, fMRI

can be used to directly measure effects of treatment on various brain areas making it potentially useful in measurements in future clinical trials (Bokde et al., 2009; Hampel et al., 2004).

1.2.3.4.2 MRI perfusion – Arterial Spin Labelling

Arterial Spin Labelling (ASL) is one technique used to measure CBF changes by using arterial blood water as a tracer by magnetically labelling arterial blood water protons (Petcharunpaisan, Ramalho, & Castillo, 2010).Compared to normal aged matched controls, AD patients appear to have up to 40% global decrease in CBF (Asllani et al., 2008). The most common areas that experience this decrease in AD are the precuneus, posterior cingulate, and superior parietal regions (Alsop, Detre, & Grossman, 2000). Additionally, it appears this occurs even in the absence of grey matter atrophy (Hu et al., 2010). Because of this, and evidence that cerebral hypoperfusion may contribute to AD, measurements of CBF may serve as a possible biomarker of AD (Wierenga, Hays, & Zlatar, 2014).

MRI perfusion studies have shown similar results to SPECT/PET perfusion and PET metabolism studies, however there is less data is available to fully assess the use of MRI perfusions as a biomarker of AD (Albert et al., 2011).

1.2.3.4.3 Diffusion Tensor Imaging

While AD is primarily considered a disease of GM, there is evidence of changes in WM as well (A. A. Gouw et al., 2008; P. Scheltens et al., 1995; C. D. Smith, Snowdon, Wang, & Markesbery, 2000). These changes are thought to be a results of axonal damage and the breakdown of oligodendrocytes and myelin in the WM (Bartzokis, 2004; Bartzokis, Lu, & Mintz, 2007; Roher et al., 2002; C. D. Smith et al., 2000). These WM changes can appear independent of GM lesions (Brun & Englund, 1986) and indications of VaD (Sjöbeck, Haglund, & Englund, 2006), and can appear in the very early stages of AD (Amlien & Fjell, 2014). These white matter changes can be measured using diffusion weighted imaging (DWI). DWI uses the diffusion of water molecules to generate contrast in magnetic resonance (MR)

images. More specifically, DTI measures the diffusion of water along axons in the WM. Because of the myelin sheaths covering the axonal fibres, water flows in a specified direction. By placing a magnetic gradient in several directions, various information about water flow through membranes of the fibres can be deducted (Barkhof, 2011). This can be used to evaluated the integrity and trajectory of the fibres (Nir et al., 2015). Diffusion based techniques have shown moderate clinical value in AD (Nir et al., 2015; Pini et al., 2016) but are less useful in cases of MCI. There are also difficulties in the reproducibility of DWI across clinical settings, making it an interesting area for further research but not a main imaging biomarker at this time (Pini et al., 2016).

1.2.3.4.4 Magnetic Resonance Spectroscopy

In-vivo quantitative measures of biochemical compounds in brain tissue can be measured using MRS or Proton MRS (^{1}H-MRS). These metabolites can reflect the neuropathological processes occurring in AD and dementia (Kantarci, 2007). The most commonly measured compounds are: N-acetylaspartate (NAA), a measure for neuronal density and function, myo-inositol (mI), a measure for astrogliosis, and choline (Cho), a measure of cell membrane degradation (Soares & Law, 2009). Levels of NAA are found to be reduced in AD, even independent of atrophy (Chao et al., 2005; Hampel, Frank, et al., 2010). Other metabolites besides NAA have not been as well studied in AD and their potential as a biomarker is debated (Hampel, Frank, et al., 2010).

1.2.4 Problems with Current Imaging Biomarkers

Imaging biomarkers are currently only officially suggested for clinical research criteria. Diagnoses are based on core clinical criteria, but imaging methods are becoming more prominent in clinical settings (G. M. McKhann et al., 2011).

There is a general difficulty in defining appropriate biomarkers because despite the advances made in recent decades in AD research, there is still a lack of firm links between the appearance of a specific biomarker and the subsequent onset of a specific clinical symptom. Biomarkers are reflections of the underlying AD pathology, but it is still difficult to know exactly to what extent the biomarkers indicate the actual pathology, and on what time scale (Sperling et al., 2011). There is pathological evidence in healthy appearing individuals, and not all patients with clinical AD symptoms experience the same pathology. Additionally, Aβ, p-tau, and t-tau proteins are not solely specific to AD and can be found in other neurological conditions. Neuronal injury is also a broad spectrum biomarker, and alone cannot indicate AD (Jack Jr. et al., 2011). Variability between biomarker measurements between different clinics and laboratories also make it difficult to determine agreed universal cut-offs for positive results (Philip Scheltens et al., 2016).

More work needs to be done to properly validate the current biomarkers, and especially on the standardisation of both protocol and outcome measures. Additionally, there is not universal access to all biomarkers across clinical communities, which can make it difficult to include them as standard practice. Moving forward, more research needs to be done comparing biomarkers, and combinations of biomarkers as often times multimodal biomarker studies are limited (Albert et al., 2011; Jack Jr. et al., 2011). There also needs to be more biomarker comparison with post-mortem studies, to see how well biomarkers actually reflect brain pathology (Jack Jr. et al., 2011).

Lastly, the validation work that has been done on current biomarkers may suffer some confounding issues. Many of these studies are done on large AD cohorts such as the Alzheimer Disease Neuroimaging Initiative (ADNI) and AddNeuroMed (Mueller et al., 2005; Simmons et al., 2011). These cohorts may suffer additional biases because they are sometimes comprised of people who volunteer that come are highly educated and come from wealthier socioeconomic backgrounds. They are also less likely to have age-related comorbidities that may also influence their cognitive decline (Sperling et al., 2011). This

would be best combated by using current biomarker techniques on the wider population, namely memory clinic samples.

1.3 Importance of Validating Research on Biomarkers: The use of Electronic Health Records

Despite the numerous advances in imaging research techniques in dementia and AD, most are not yet applied to the clinic and are only used in research or clinical trial settings. There are a variety of cohort types, each with their own advantages and disadvantages.

Ideally, a sample selected completely at random, would be used for all studies. A random selection from a source that is reflective of the general population (for example an electoral roll), will most closely reflect the general population and therefore have the most generalisable results and highest external validity (Hulley, Cummings, Browner, Grady, & Newman, 2013). It is important to remember that no sample is completely representative, as participation is always voluntary and in theory there could be fundamental differences in those willing to volunteer versus those who are not (the so-called "volunteer gene") (L. J. Launer, Wind, & Deeg, 1994). Lastly, even registers are not fully representative as they do not include illegal immigrants or people who move often. Lastly, while population samples are ideal to study highly prevalent disorders and their impact on the population, it is the most complicated and expensive method which means it may not be appropriate when studying a rare disease, or when resources are minimal.

Convenience samples are quicker, easier, and more economical than population samples. The selection of people is based on the ease of recruitment, and may not be reflective of the entire population. These samples usually share a characteristic from an epidemiological point, but are still heterogenous. Community-based volunteer samples are convenience samples recruited through advertisements or

word of mouth. The more restricted the advertising is to specific groups (for example, in a care home) the more biased the resulting sample will be. Volunteers tend to have a higher educational level, better socioeconomic status, and a particular interest in the issue being studied, in addition to the previously discussed potential fundamental differences in those who volunteer versus those who do not (Rosenthal & Rosnow, 1975). Secondly, there could be clinical (or medical help-seeking) convenience samples. These are samples recruited from general practitioners or more specialised clinics that usually require a referral to the service (such as the memory clinic used for the studies in this PhD). Lastly, samples can be mixed, for example a group of controls recruited from ads (community-based) and a patient population from a clinic. However, these mixed samples may exaggerate differences between clinical samples and healthy controls (Brodaty et al., 2014).

In the context of AD, differences in rates of decline in convenience based samples (such as ADNI) and population based (such as the mayo clinic) in AD may not be representative of the general population (Jennifer L. Whitwell et al., 2012). On average, the mayo clinic sample (population based) was older, less educated, had less familial history of AD, lower MMSE, smaller hippocampal volume in controls, and less likely to have the APOE e4 allele (in the amnestic MCI category). These biases could be due to recruitment methods, where healthy subjects worried about their cognition may be more motivated to answer advertisements or go to a memory clinic in the first place (where the study is advertised). Additionally, those with higher education are more likely to seek medical help or become involved in observational studies.

Similarly to the aforementioned cohorts, clinical trials may also suffer from analogous biases because often times participants are more affluent, have higher levels of education, and may lack other comorbidities that the general public suffer from. While these stratified samples are arguably very useful for conducting research, there must be studies examining these techniques and their effectiveness in the general population.

1.3.1 Integration of Electronic Health Records and Neuroimaging

Both medical professionals and researchers have concluded that there is a very strong opportunity for studies with clinical cohorts and even population-wide research that may aid in bridging the translational gap between research and clinical practice through the use of sharing electronic health records (Jensen, Jensen, & Brunak, 2012).

1.3.1.1 Electronic Health Record use in Research and Clinics

Electronic health records (EHRs) are becoming a popular alternative to traditional hand written records in clinics and hospitals across the globe. Largely, this is due to the rapid improvements in technology and information storage in the last few decades. Various initiatives across the world have increased the use of EHRs. The HITECH act (Blumenthal, 2010) in the United states had provided $19 billion and the public-private partnership Innovative Medicines Initiative (IMI) has put forward €2 billion in the European Union in order to grow and implement these technologies (Goldman, Seigneuret, & Eichler, 2015; Hunter, 2008). There are a variety of national strategies devoted to the development and implementation of interoperable health information technology systems and EHRs (Coiera, 2009; Morrison, Robertson, Cresswell, Crowe, & Sheikh, 2011). The main focus of these developments has been more comprehensive patient care, but the applicability extends far past that.

There are many benefits to using an EHR system instead of a paper-based one. EHRs can ideally provide an inclusive historical overview of a patient's history in one easily accessible place. Undoubtedly, this depends on the integration of GP and hospital records. Ideally, information can include, but is not limited to demographics, past medical and visit history, allergies, medications, and laboratory and radiology reports. An EHR system provides a structured template, creating a more standardised system with all patients having the same information. Having an electronic system facilitates sharing of information between medical professionals at different hospitals and clinics. Shared information allows

for more efficient and safe care by avoiding medical errors due to drug interactions, allergic reactions, and other potential issues. Additionally, implementation of EHRs have been shown to increase efficiency in health care delivery by avoiding the waste of resources (both supplies and manpower), such as redundant testing (Institute of Medicine (US) Committee on Quality of Health Care in America, 2001). Overall clinicians appear to prefer it and recognize the potential benefits of an electronic system (Menachemi, Powers, & Brooks, 2009; Mistry & Sauer, 2009).

Conversely, there are a number of issues that arise with the use of an EHR system. Many of these issues stem from the initial implementation of a new system such as loss of productivity, disruption of normal workflow, and extra financial burden (Menachemi & Collum, 2011). These are usually temporary problems that result from installing and learning a new system. More longstanding problems include the maintenance costs associated with continued use, which are incurred with hardware replacement and software updates. Perhaps the biggest drawback of switching to an EHR system is the potential risk of privacy violations of patients.

Beyond the arena of clinical care, EHR systems create a myriad of opportunities for research within clinical settings. Firstly, EHRs help to create an enormous database of information, allowing the potential for researchers to gather information about disease comorbidities, effectiveness of medications, and more (Jensen et al., 2012). The electronic nature of the system allows more widespread accessibility to researchers interested in specific disorders and conditions. Additionally, the data is usually structured in a more unified way making it easier for researchers to acquire any relevant data from one single source, than paper records. A challenge of this is mining the aggregated data in meaningful ways despite the inherent differences in the data as free text clinical description, diagnostic codes, physiological data, and radiological results are all presented and stored very differently. This combination of data however, provides an interesting opportunity for researchers to discover potential

relationships with an extremely great variety of variables. This makes EHR systems both a prime area for disease specific and small sample research, and larger, more exploratory analyses.

2 THE BIOMEDICAL RESEARCH CENTRE MEMORY CLINIC COHORT

The main focus of this thesis is the translation of advanced imaging techniques from research based cohorts to clinical cohorts. This is a crucial step in validating analysis methods as potential biomarkers, which is needed in order to use these techniques in clinical practice (G. M. McKhann et al., 2011). Advances in scientific technologies have now allowed us to visualise more of pathology in Alzheimer's Disease (AD) and dementia, which can be extremely helpful in the diagnostic process. This chapter will describe the memory clinic cohort that was used in the following studies aimed at the translation of research techniques into the clinic.

2.1 BIOMEDICAL RESEARCH CENTRE MEMORY CLINIC COHORT

The Biomedical Research Centre memory clinic cohort (BRCMEM) is a continuously ongoing research initiative run by the NIHR Maudsley Biomedical Research Centre and Dementia Unit (BRC/U), which is a collaborative partnership between the South London and Maudsley (SLaM) NHS Foundation Trust and the Institute of Psychiatry, Psychology & Neuroscience at King's College London. The aim of the BRC is to explore experimental medicine and translational research to introduce the latest research techniques into the mental health clinics. The group brings together researchers, clinicians, allied health professionals and service users across the university and NHS trust partnership to work together to improve care for patients.

The BRCMEM cohort was designed based on the AddNeuroMed cohort (Lovestone et al., 2009), and uses the same scanning parameters described later for accurate comparability in future studies. The goal of this project was to follow clinical patients going through a dementia diagnosis assessment using one of SLaM's memory services, and use the already available information to develop better clinical

imaging techniques for dementia and AD, examine new and existing biomarkers, and explore the feasibility of incorporating electronic health records (EHRs) for research purposes.

As of February 16, 2017 there are 2,712 subjects in the BRCMEM cohort. For the purpose of this PhD, only the first 1,000 subjects were used in analyses. These participants were scanned between January 2011 and May 2014.

2.1.1 Demographics

2.1.1.1 The SLaM Cohort

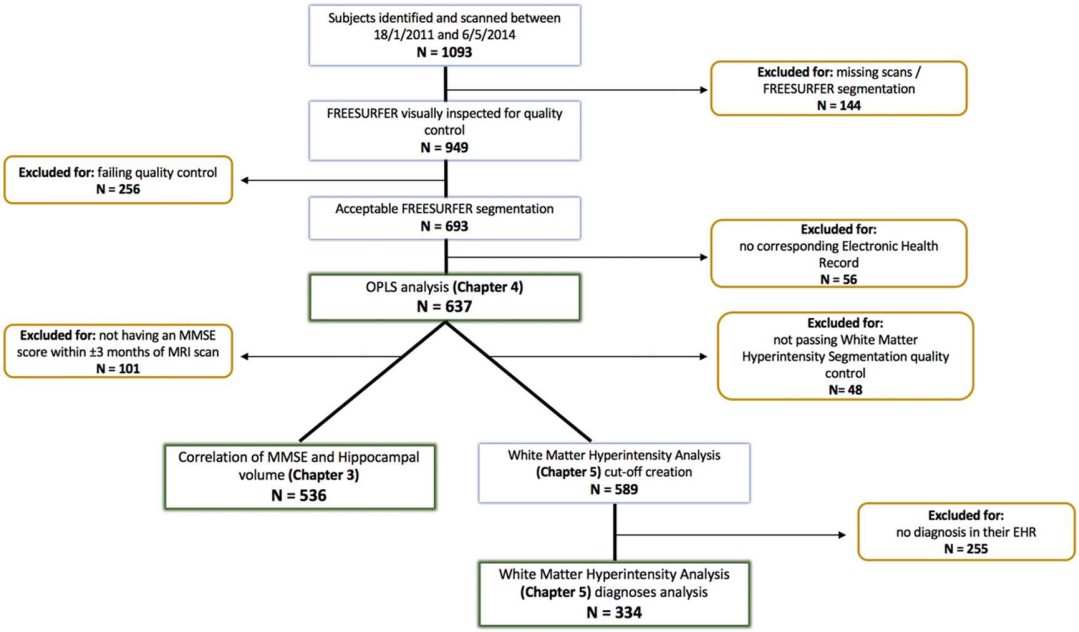
SLaM covers over 1.2 million people in four major south London boroughs (Southwark, Lambeth, Croydon, and Lewisham). SLaM is currently structured with a variety of specialty groups including: Addictions, Behavioural & Developmental Psychiatry, Child & adolescent Mental Health Services, Mental Health of Older Adults & Dementia, Mood, Anxiety & Personality, Psychological Medicine, and Psychosis. SLaM also provides wider national provisions such as adult attention deficit hyperactivity disorder, adult personality disorder, anxiety disorders, autism assessment and behavioural genetics, brain injury (both outpatient and inpatient), chronic fatigue, eating disorders, female hormone clinic, mother and baby unit, autism, practitioner health, psychological interventions, psychosexual disorders, self-harm, and traumatic stress.

2.1.1.2 The Memory Clinic Cohort

The memory clinic cohort includes any patients that have been referred to one of the trusts participating memory clinics: Croydon Memory Service, Lewisham Memory Service, or Southwark and Lambeth Memory Service. Out of the first 1,000 participants of the memory clinic, we were able to connect 934 with their EHRs, as described in subsequent sections. Out of the total 934 participants, 538 were female and 396 were male. The average age of participants at the time of their scan was 74.44 (std = 10.147), with a wide age range from 28-97 (Table 2-1). While the younger ages are very unusual for any kind of

dementia or AD, these patients were referred to one of the memory clinics by their GP and were therefore included in all of the studies and analyses. As described later, many of the analyses were broken down by diagnosis, and therefore we did not see this as a limitation. Majority of participants (566; 60.6%) identified as British, with the second most common ethnicity being Caribbean (106; 11.3%). A full breakdown of the number of participants used in each study, and reasons for exclusion are included in Figure 2-1.

Figure 2-1 *A full breakdown of participants used in each of the studies, including reasons for exclusion*



2.2 METHODS

2.2.1 Inclusion Criteria

In order to be eligible to participate, subjects must have been referred to one of the SLaM memory clinics for suspected dementia. All health records from SLaM patients are funnelled into the Clinical Record Interactive Search (CRIS) system and there is an opt-out option available. There must be significant impairment of daily activities consistent with a diagnosis of mild to moderate dementia or

Mild Cognitive Impairment (MCI). Because all participants were referred to SLaM memory clinics, all records were present on the hospital's EHR system and therefore accessible by CRIS. As of February 16, 2017, there are 2,712 subjects in the cohort. For the purpose of this study, we decided to use the first 1,000 subjects.

2.2.2 MRI Acquisition

As per standard examination in the SLaM memory clinics, all participants received a standard T1-weighted MPRAGE volumetric structural scan, a T2 Fluid attenuation inversion recovery (FLAIR) propeller and T2 propeller scan. T1 weighted scans are known for high spatial resolution and good grey matter and white matter contrast, and are particularly good for visualizing atrophy. FLAIR scans have an inversion time such that the signal of water in the scan is suppressed. This gives the scan low white-grey matter contrast, which allows visualisation of lesions in cortical and subcortical regions (Barkhof, 2011). Lastly, T2 weighted scans result in very high signal of cerebrospinal fluid (CSF) compared to the other tissues, and is particularly useful for observing tissue oedema and lesions.

Scans were acquired using a 1.5T GE Signa HDx system, using the ADNI-1 (Clifford R. Jack, Bernstein, et al., 2008) and AddNeuroMed (Lovestone et al., 2009; Simmons et al., 2011) acquisition parameters. The 3D T1-weighted MPRAGE images were acquired using a magnetization-prepared rapid gradient echo sequence (MPRAGE) using the following: TE = 3.8 ms, TR = 8.592 ms, TI = 1000 ms, matrix size 192x192, flip angle 8^{o}, FoV = 240 mm, voxel dimension .9375 x .9375 x 1.2 mm. Full brain and skull coverage was required for the MRI datasets and detailed quality control carried out on all MR images from both studies according to previously published quality control criteria (Simmons et al., 2009, 2011) which included ensuring there was no wrap-around artefacts affecting the brain, motion artefacts, image inhomogeneity, or inadequate contrast between grey and white matter. Any images that did not pass visual inspection quality control were not included in further analyses.

2.2.3 Cognitive Testing

As per standard practice, any patients (and/or carers) accepted to the memory clinic are interviewed in an initial assessment. This initial interview is designed to measure cognitive and functional assessment, and is given by a doctor, nurse, psychologist, occupational therapist, or social worker trained in dementia diagnosis. The assessment includes cognitive concerns, mental state and symptoms, daily functioning and psychopathology, and personal, educational, family and medical history. Additionally, a variety of cognitive exams are administered, which may include: Addenbrooke's cognitive examination (ACE), the standardised mini-mental state examination (MMSE), Neuropsychiatric Inventory (NPI), Bristol Activities of Daily Life Scale, the Geriatric Depression Scale (GDS), and Geriatric Anxiety Inventory. Results from this initial interview are discussed with the multi-disciplinary memory service team to determine further assessment and treatment.

Assessments may be redone with follow up appointments over time, for example after six or twelve months. All results from initial and follow-up cognitive testing are listed in the memory clinic patient's electronic health records.

2.2.4 Consent

This study includes patients from the SLaM Trust, who were referred to one of the trust's participating memory clinics. Patients were asked if they would authorise use of their anonymised MRI images for research purposes. Consent forms are included on every safety form, and all participants scanned for any reason are asked if they would allow their MRI images to be used, regardless of reason of visit. In order to be eligible to participate, subjects must have been referred to one of the SLaM memory clinics for suspected dementia. All health records from SLaM patients are funnelled into the Clinical Record Interactive Search (CRIS) system and there is an opt-out option available, as described in the next section. There must be significant impairment of daily activities consistent with a diagnosis of mild to

moderate dementia or MCI. Because all participants were referred to SLaM memory clinics, all records were present on the electronic Patient Journey System (PJS) and therefore accessible by CRIS.

Ethical approval for this study was granted by the National Health Service (NHS) Health Research Authority (09/H0606/84).

2.3 STRENGTH OF THE BRCMEM COHORT

While there has been significant advancement in the diagnostics of AD and dementia in the last few years, it has been acknowledged that many research studies suffer from cohort biases (Sperling et al., 2011). Biomarker and cognitive studies, the most popular types of studies in AD, may not be based on cohorts that are truly representative of the older population. The majority of these cohorts are made up of people who are willing to volunteer for MRI research, which tend to be highly educated and come from higher socioeconomic backgrounds. As they have been described by Sperling et. al, they may be considered samples of convenience and have the so-called "volunteer gene", and be more active than typical of other people that age (Sperling et al., 2011). Additionally, due to specific exclusion and inclusion criteria, these subjects are less likely to have typical age-related comorbidities that could influence cognitive decline.

This PhD aims to combat these potential biases in previous dementia studies by using a clinical cohort. The SLaM memory services cover a wide catchment area that serves a variety of people across education levels and socioeconomic backgrounds. Because these patients are already present for their scan, and only need to sign a consent form included on their MRI safety sheet to indicate whether or not, the bias of the "volunteer gene" is most likely not present, as these people were not actively seeking to participate in research. Lastly, all patients referred to one of the memory clinics are included in this cohort. There are no restrictions based on a specific type of dementia diagnosis, or other comorbidities that may contribute to their cognitive decline. The hope is that current research

techniques provide inside into potential new diagnostic tools that are just as effect in the clinic as they are in research-based cohorts.

3 CORRELATION OF MMSE SCORE AND HIPPOCAMPAL VOLUME IN A MEMORY CLINIC COHORT

3.1 INTRODUCTION

3.1.1 The Mini Mental State Examination

The Mini Mental State Examination (MMSE) is the most commonly used cognitive test for patients experiencing memory deficiencies (Arevalo-Rodriguez et al., 2015), and is widely used for diagnosing Alzheimer's Disease (AD) and dementia. In addition to being used widely across clinical settings, it is also one of the most commonly used neuropsychological assessments in dementia research. The MMSE gives insight to the severity of cognitive decline amongst patients and participants, but is not sufficient to make a diagnosis alone.

3.1.2 Hippocampal Volume and Dementia

Hippocampal atrophy is a characteristic feature of AD and can even be evident in patients with Mild Cognitive Impairment (MCI) as well. Hippocampal volume, and thus hippocampal atrophy, can be measured using structural MRI. Hippocampal atrophy has been found to be predictive of further cognitive decline and dementia (Clifford R. Jack et al., 1999; P. J. Visser et al., 1999). Because hippocampal atrophy can be reflective of memory deficits (Schröder & Pantel, 2016; Wolf et al., 2001), it is likely to be correlated with MMSE score. Indeed, this has been demonstrated in a variety of studies both looking at AD and dementia (C.R. Jack et al., 2002; Peng et al., 2015; Yavuz et al., 2007) and other conditions (Sawyer, Corsentino, Sachs-Ericsson, & Steffens, 2012; Steffens et al., 2002).

3.1.3 Rationale and Hypotheses

The goal of this study was to integrate EHR and automated analysis of clinical neuroimaging for the first time. As a specific initial exemplar to examine the feasibility of attaching EHR data with automated MRI results from clinical imaging, the correlation between hippocampal volume and MMSE score was examined. Based on past research, it is expected that MMSE score will be positively correlated with hippocampal volume. Within a clinical setting, it would be useful for clinicians to have access to relevant data aside from the images themselves, such as volumetric measurements listed previously. However, potentially more importantly, this repository of information allows researchers to have access to wider samples of a clinical nature. Allowing researchers access to clinical samples is a vital part of translating research into the clinic.

3.2 METHODS

3.2.1 Memory Clinic Cohort

As previously described, the memory clinic cohort includes any patients that have been referred to one of the trusts participating memory clinics: Croydon Memory Service, Lewisham Memory Service, or Southwark and Lambeth Memory Service. From our original sample, 536 participants had an MMSE score within ± 3 months of a structural MRI scan that passed quality control. This subset included 217 males and 319 females.

3.2.2 Electronic Health Records

EHR linkage has been done for research purposes, not in conjunction with neuroimaging data. This section describes the procedures done to create the EHR database used. While this database creation was not specifically for this PhD, it was an integral part of the analyses. The following section (*3.2.2*

Electronic Health Records) is based on the work by Stewart, Fernandes, and colleagues (Fernandes et al., 2013; Stewart et al., 2009)

3.2.2.1 The South London Mausley Hospital & Clinical Record Interactive Search System

The South London and Madusley (SLaM) National Health Service (NHS) Foundation trust is one of the largest mental health care providers in Europe, servicing a catchment area of over 1.2 million residents over four south London boroughs (Croydon, Lambeth, Lewisham, and Southwark) in addition to some specialist services at a regional/national level. All patient records at SLaM have been paperless since April 2006, when the trust's electronic Patient Journey System (PJS) was introduced. The PJS is a comprehensive electronic health record system, unique to SLaM, that follows the patient's journey through the trust's services and includes all relevant clinical information such as: demographic and contact information, dates of referrals and transfers, detailed clinical assessments, care plans, medication, and clinical activity and reviews. It consists of both structured field based data and unstructured free text – including assessments, progress notes, and correspondence. This database is used and maintained by a variety of healthcare professionals throughout the trust.

The Clinical Record Interactive Search (CRIS) system was created in order to provide an anonymized database for clinical auditing and research purposes. It pulls records directly from the trust's PJS. The system is representative of all of SLaM care, including all patients' records. An opt-out system is available and advertised publicly but as of 2013 only three people had requested this (Perera et al., 2016). CRIS allows researchers and clinicians to specify criteria to define the cohort of interest, such as those with a specific diagnosis or that contain a keyword of interest. Once a cohort of interest is specified, clinicians and researchers can then decide what variables are of interest, such as clinical status or trust movement. The CRIS system then returns anonymised records of relevant participants, with any variables that were deemed important. In addition, CRIS links with a variety of resources such as the

Mental Health Minimum Dataset, Hospital Episode Statistics (HES) for England and Wales, Primary Care information (Lambeth DataNet), the Department of Education National Pupil Database, and the Office for National Statistics (ONS) for mortality data, creating an even more powerful database. As of 31 December 2014 there were more than 250,000 clinical records accessible on the CRIS system (Perera et al., 2016).

CRIS uses a dual de-identification algorithm and security model to ensure patients' anonymity is protected. This is especially important in psychiatric case registers because the nature of the data is potentially stigmatising. In order to create the data store of de-identified records linked directly to PJS, a systematic process was followed to mask all potentially personally identifying information - designated as personal identifiers (PIs). The Health Insurance Portability and Accountability Act (HIPAA) in the United States lists 18 different PIs that must be masked in order to use health records in research (Malin, Benitez, & Masys, 2011; Neamatullah et al., 2008). The UK does not have specific stipulations on the types of information that need to be masked, but do encourage appropriate de-identification based on context (The Academy of Medical Sciences, 2006). In the UK, each NHS trust is assigned a "Caldicott Guardian" and committee which represents both clinical and service users. The main duty of the Caldicott Guardian is to guarantee patient confidentiality within their specified trust (Greenough & Graham, 2004).

3.2.2.2 De-identification Process

Any information input on the HTML front-end of PJS is processed and stored in a secure Structured Query Language (SQL) database, which is continually updated as new information is entered into PJS by clinicians or other relevant service users. CRIS was built in partnership with BearingPoint™ and uses FAST™ search technology. Before data can be searched via the CRIS system, the data from PJS must be converted into Extensible Mark-up Language (XML). All content is extracted from a replicated SQL Server

using a custom program called SQL extractor in order to convert this data in to XML. The SQL extractor code then generates one XML document per patient, storing relevant clinical information in this document while maintaining the tiered structure found on PJS. Once source SQL data has been extracted and formatted accordingly, the records are then stored on a disk before they are passed to FAST for ingesting, eventually providing a searchable index. XML records are modified during this process using a transformation pipeline. This pipeline, written in Python, is accessed from within FAST. The de-identification process is handled by two pipeline stages which determine not only what needs to be removed from the XML but also where in the XML any PI content can be found. The process is as follows:

1) A list of fields is created that contains PIs. In this list both field name and field type are defined. Field type will later define how the algorithm treats the field when adding it to the cleaning dictionary (what will be removed later on). A field is either a) added to the dictionary and completely stripped from CRIS (for example, the patient's name) or is b) added to the dictionary and truncated in CRIS (for example, the last three characters of the patient's post code are stripped from CRIS) as to protect the identity of the patient yet retain relevant geographical information. This differs from other de-identification algorithms as the cleaning dictionary isn't obtained from registries (Meystre, Friedlin, South, Shen, & Samore, 2010) but directly from the patient forms on the EHRs themselves. This creates a cleaning dictionary that is unique for each patient and includes: first names, last names, middle names, nicknames, contact numbers, key person contacts, addresses, trust IDs, and date of birth. Additionally, copies of the PIs are stripped of delimiters (such as apostrophes or hyphens) and also added to the cleaning dictionary. (Table 3-1)
2) To save time on processing, the de-identification algorithm is not run on the entire XML file but instead on specific predefined areas delineated through the use of *XML tags* or *XML scopes.*

These tags are used to by the program to determine where the de-identification algorithm is necessary. This includes any free text entries, such as case notes and summaries and core patient info and summary fields.

3) A masking string is used to replace words that have been identified as to be removed. Direct patient identifiers replaced with a ZZZZZ string while relative or close contact identifiers are replaced with QQQQQQ in order to not confuse who the entered information belongs to.
4) A list of address aliases is created in order to ensure things that are not entered identically to what is in the address field, such as road/rd and street/st, are still masked.

Using the above processes, the python code uses the newly configured fields to populate the cleaning dictionary. Heuristics are used to identify different PI formats or patterns, such as a telephone number being written as 00000-000-000 or 00000000000, which is particularly useful for free-text fields. Once the cleaning dictionary is complete the python code reads the XML tags to determine what information within the tags needs to be removed. This is done based on a set of rules to determine where each token of PI begins and ends. Once a token is identified, it is compared against the cleaning dictionary. If there is a match it is replaced with the appropriate masking string. The code is flexible, and fields or tags can be added without changing the underlying code.

Table 3-1 – *List of example personal identifiers (PIs) and cleaning dictionary. * an actual CRIS cleaning dictionary would include more variations on date of birth etc; and this example list is not exhaustive but for illustrative purposes. Adapted from Fernandes et al. 2013.*

Example Patient Information	
First Name	Charles
Middle Name	(blank)
Second Name	Smith
Date of Birth	24/03/1990
Trust ID	12-34-56
Post Code	SW4 XLT
Nick Name	Charlie
Key Contact	Barrett
Example Cleaning Dictionary from above information*	
Charles	
Smith	
24/03/1990	
24/03/90	
24-03-1990	
24-03-90	
24.03.1990	
24.03.90	
24th Mar 1990	
24th of Mar 90	
24 March 1990	
24 Mar 1990	
12-34-56	
12 34 56	
123456	
SW4 XLT	
SW4XLT	
Barrett	

3.2.2.3 Security Model

In addition to the de-identification process, a multifaceted security model was developed in order to address the ethical and legal considerations that come along with using patients' confidential data and records. The first in this process was the development of the CRIS Oversight Committee which is chaired by a mental health service user, and also includes a child and adolescent mental health clinical

representative, a representative of the Trust's Caldicott Guardian, a Research Ethics representative, and the CRIS academic project lead and CRIS project manager.

Use of the CRIS system is application based, meaning researchers must submit an application to the oversight committee detailing their project and variables of interest. If the application is to conduct an audit of clinical services within the trust, it will be presented to the relevant audit committee within SLaM before being reviewed by the CRIS Oversight Committee. Projects that are researcher based must have a senior university or NHS affiliated supervisor to take responsibility for the project before it is viewed by the oversight committee. All applicants must have affiliation with the trust in the form of an honorary or substantive contract with the hospital or university previous to applying for CRIS, which in turn formally hold the applicant to the NHS duty of confidentiality. Applications are assessed based on the suitability by evaluating the need for the project and scientific robustness of application. Any potential confidentiality concerns are identified, and if there is a potential to identify patients these concerns are discussed with both the researcher and their supervisor. Potential alternatives, such as obtaining patient consent, are presented if possible.

Once an application is accepted by the oversight committee, researchers are required to access CRIS only within the SLaM security firewall. Users must follow specific rules to ensure responsible handling of data and guarantee confidentiality of the patients. Projects are audited on a weekly basis, and if projects are being carried out inappropriately approval can be revoked. This close examination of ongoing projects and strict regulation of access to CRIS ensure data handling obeys the guidelines set out by CRIS, and safeguard the anonymity of patients within the trust.

3.2.3 Hippocampal volume analysis

3.2.3.1 FREESURFER automated volumetric analysis

The T1 images were analysed with the FREESURFER pipeline version 5.3.0 (http://surfer.nmr.mgh.harvard.edu/), which includes removal of non-brain tissue using a hybrid watershed/surface deformation procedure (F. Ségonne et al., 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep grey matter volumetric structures (Bruce Fischl et al., 2002; Bruce Fischl, Salat, et al., 2004; F. Ségonne et al., 2004) intensity normalization (Sled, Zijdenbos, & Evans, 1998), tessellation of the grey matter white matter boundary, automated topology correction (B. Fischl, Liu, & Dale, 2001; Ségonne, Pacheco, & Fischl, 2007), and surface deformation following intensity gradients to optimally place the grey/white and grey/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (A. M. Dale, Fischl, & Sereno, 1999; Anders M. Dale & Sereno, 1993; B. Fischl & Dale, 2000). Once the cortical models are complete, registration to a spherical atlas takes place which utilizes individual cortical folding patterns to match cortical geometry across subjects (B. Fischl, Sereno, Tootell, & Dale, 1999). This is followed by parcellation of the cerebral cortex into units based on gyral and sulcal structure (Desikan et al., 2006; Bruce Fischl, van der Kouwe, et al., 2004). The pipeline generated 68 cortical thickness, cortical volume, surface area, mean curvature, gaussian curvature, folding index and curvature index measures (34 from each hemisphere) and 21 regional subcortical volumes (Table 3-2). This segmentation approach has been used for multivariate classification of Alzheimer's disease and healthy controls (Westman, Wahlund, Foy, et al., 2011), neuropsychological-image analysis (Yawu Liu, Paajanen, Zhang, et al., 2010; Yawu Liu et al., 2011), imaging-genetic analysis (Yawu Liu, Paajanen, Westman, Wahlund, et al., 2010; Yawu Liu, Paajanen, Westman, Zhang, et al., 2010) and biomarker discovery (Thambisetty et al., 2010). For the purpose of this study, only left and right hippocampal volumes were used, but all other data is available.

All FREESURFER segmentation outputs were visually inspected by myself. During my undergraduate degree, I was trained in manual hippocampal segmentation in the lab of Dr. Jens Pruessner, and it was therefore decided that my anatomical knowledge of the hippocampus would be sufficient as a quality control of the FREESURFER segmentation outputs.

Table 3-2 *- List of FREESURFER outputs, including all Cortical Thicknesses and Subcortical structures used in the OPLS analysis*

Cortical Thicknesses (both Right and Left)	Subcortical structures
Banks of superior temporal sulcus	Third ventricle
Caudal anterior cingulate	Fourth ventricle
Caudal middle frontal gyrus	Brainstem
Cuneus cortex	Corpus callosum anterior
Entorhinal cortex	Corpus callosum central
Fusiform gyrus	Corpus callosum midanterior
Inferior parietal cortex	Corpus callosum midposterior
Inferior temporal gyrus	Corpus callosum posterior
Isthmus of cingulate cortex	CSF
Lateral occipital cortex	Accumbens
Lateral orbitofrontal cortex	Amygdala
Lingual gyrus	Caudate
Medial orbitofrontal cortex	Cerebellum cortex
Middle temporal gyrus	Cerebellum white matter
Parahippocampal gyrus	Hippocampus
Paracentral sulcus	Inferior lateral ventricle
Frontal operculum	Putamen
Orbital operculum	Lateral ventricle
Triangular part of inferior frontal gyrus	Pallidum
Pericalcarine cortex	Thalamus proper
Postcentral gyrus	Ventral DC
Posterior cingulate cortex	
Precentral gyrus	
Precuneus cortex	
Rostral anterior cingulate cortex	
Rostral middle frontal gyrus	
Superior frontal gyrus	
Superior parietal gyrus	
Superior temporal gyrus	
Supramarginal gyrus	
Frontal pole	
Temporal pole	
Transverse temporal cortex	
Insular	

3.2.3.2 Hippocampal Volume Normalisation

Hippocampal volumes used in the analysis were normalised by total intracranial volume (ICV) as determined by FREESURFER segmentation, to control for differences in head size. This was done by creating a ratio of hippocampal volume divided by total ICV, to remain consistent with other studies from our group. This has been found to be essential in 67 structural MRI studies, as differences in head size can create gender differences and influence the results (Scahill et al., 2003; J. L. Whitwell, Crum, Watt, & Fox, 2001). It has also been found that method used for both ICV volume estimation (Nordenskjöld et al., 2013), and ICV volume correction can yield different results (Arndt, Cohen, Alliger, Swayze, & Andreasen, 1991; Barnes et al., 2010; Malone et al., 2015; O'Brien et al., 2011), and therefore results must be interpreted with this limitation in mind.

3.2.4 Statistical Analysis

All statistical analyses were performed with SPSS 21 software package, and considered significant at the $P < 0.05$ level.

3.2.4.1 Memory Clinic Cohort

From our original sample, 536 participants that had an MMSE score within ± 3 months of a structural MRI scan that passed quality control. This subset included 217 males and 319 females. To test for group differences between genders, average MMSE score, normalised hippocampal volumes, and age were calculated for each gender. One-way Analysis of variance (ANOVA) was used to examine if significant differences existed between the genders.

The memory clinic was further broken down by ultimate diagnosis found in their EHRS. Of the 536 participants, 419 had a diagnosis listed on their clinical record. These subjects were then placed into one of the following categories: AD, MCI, Vascular Dementia (VaD), Mixed Dementia (MD), other dementia (such as dementia from Parkinson's or Dementia in Pick's disease), unspecified dementia, other

psychiatric disorder (such as depression or anxiety), and no diagnosis (such as person with mental health complaints). Group differences between age, average MMSE, and average total normalised hippocampal volume were measured using a one-way ANOVA, with Bonferroni corrected post-hoc tests.

3.2.4.2 MMSE and Hippocampal Volume Correlation

Pearson partial correlation of MMSE score and combined normalised hippocampal volume (right + left hippocampal volume / total ICV), while controlling for age at the time of scan, was run on the entire set of participants.

Correlations between MMSE and hippocampal volume while controlling for age were calculated for each diagnostic group (AD, MCI, VaD, MD, other, and unspecified dementia) with a dementia related diagnosis. Normalised volumes for each the right and left hippocampus were created, and correlated with MMSE score as well.

3.3 RESULTS

3.3.1 Memory Clinic Cohort

536 participants were used in this analysis, out of the original cohort of 934. The average age at scan was 78.82 years, with no significant differences between the age of males and females. The average MMSE score of the cohort was 23.35, again with no significant differences between males and females (Table 3-3). There were significant differences between male and female normalised hippocampal volumes, but this is to be expected as this is found in the literature (Nordenskjöld et al., 2015; Voevodskaya et al., 2014). The memory clinic was further broken down by ultimate diagnosis found in their EHRS, and as expected there were many significant differences between age, average MMSE, and average total normalised hippocampal volume between the groups (Table 3-4). Because of the abundance of information, this data is included as Appendix 1.

Table 3-1 – *Memory Clinic Cohort Demographics. Age, Normalised HC Volume, and MMSE score = Mean (Standard Deviation). Gender differences between Age, Normalised HC Volume, and MMSE score were measure by ANOVA. * denotes mean difference between genders significant a p<0.05 level.*

	Number	Age	Normalised HC Volume	MMSE
Memory Clinic	536	78.82 (10.23)	.00409 (.001)	23.35 (5.14)
Females	319	78.55 (10.57)	.00417 (.001)*	23.17 (5.12)
Males	217	79.21 (9.72)	.00397 (.001)*	23.61 (5.16)

3.3.2 MMSE and Hippocampal Volume

Patients were broken down to sub groups based on diagnosis which included AD, MCI, MD, VaD, other form of dementia, and other psychiatric condition or no diagnosis. AD patients revealed the strongest correlation (r=.198, p=.009) (Figure 3-1). Patients in the VaD, MCI, and MD groups did not display a significant correlation between MMSE and normalised hippocampal volume (Table 3-4).

Figure 3-1 – *Scatter-plot of MMSE and Total (Left + Right) Normalised Hippocampal Volume for only patients in the memory clinic cohort. A. Alzheimer's Disease B. Mild Cognitive Impairment C. Mixed Dementia D. Vascular Dementia E. Unspecified Dementia and F. Other type of dementia*

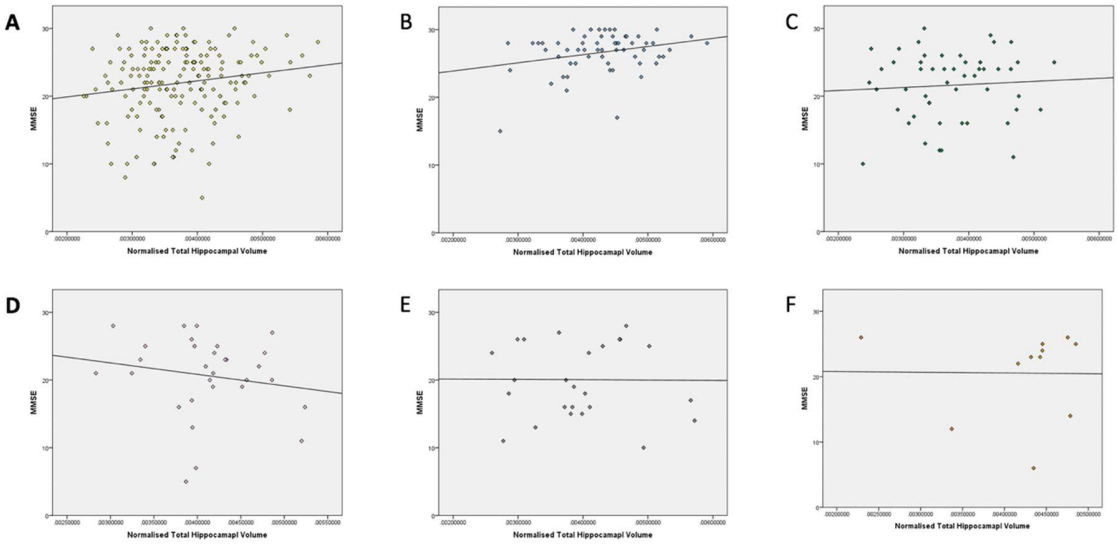


Table 3-2 – *Correlation between MMSE score and total normalised hippocampal volume. Broken down by diagnostic category. Age, MMSE, and normalised HC volume = Mean (Standard Deviation). * Denotes significant correlation at p < 0.05 level*

Disease Group	Number	Age	MMSE	Total Normalised HC volume	R – Correlation	P-value
Alzheimer's Disease	175	82.04 (7.80)	21.95 (5.11)	.00374 (.001)	.198	.009*
Mild Cognitive Impairment	59	79.68 (7.16)	26.64 (2.95)	.00429 (.001)	.185	.164
Vascular Dementia	30	81.99 (7.62)	20.63 (5.80)	.00412 (.001)	-.212	.271
Mixed Dementia	51	83.33 (7.12)	21.61 (4.96)	.00373 (.001)	.113	.435
Unspecified Dementia	26	79.97 (9.08)	20.04 (5.80)	.00397 (.001)	-.082	.696
Other Dementia	11	75.22 (8.20)	20.55 (6.73)	.00420 (.001)	-.090	.804
Other Psychiatric Disorder	51	71.96 (11.89)	23.96 (5.13)	.00449 (.001)	-	-
No Diagnosis	16	78.47 (7.79)	26.06 (2.84)	.00373 (.001)	-	-
Diagnosis not listed	117	73.90 (12.77)	25.61 (3.88)	.00457 (.001)	-	-

Furthermore, MMSE was correlated with each side of the hippocampus individually. The normalised volumes for the left hippocampus were more highly correlated than the right hippocampus across the AD (left HC: r=.224, p=.003 – Figure 3-4; right HC: r=.150, p=.048 – Figure 3-5) and AD + MCI groups (left HC: r=.305, p<.001; right HC: r=.253, p<.041), which was not seen for the other dementia subtypes (Table 3-5).

Figure 3-2 *– Scatter-plot of MMSE and Normalised Left Hippocampal Volume for only AD patients in the memory clinic cohort (N=175). Pearson's R =.224, p=.003.*

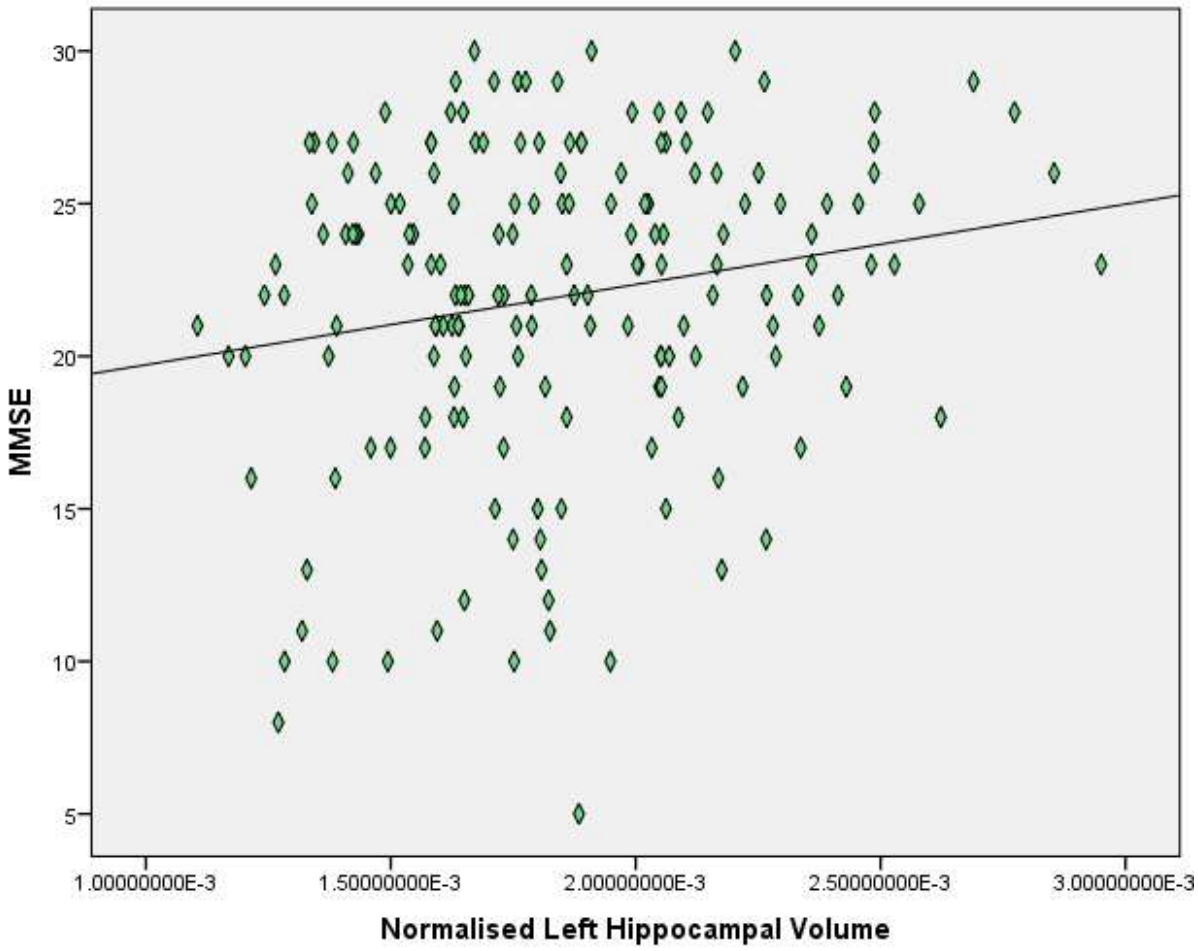


Figure 3-3 *– Scatter-plot of MMSE and Normalised Right Hippocampal Volume for only AD patients in the memory clinic cohort (N=175). Pearson's R =.150, p=.048.*

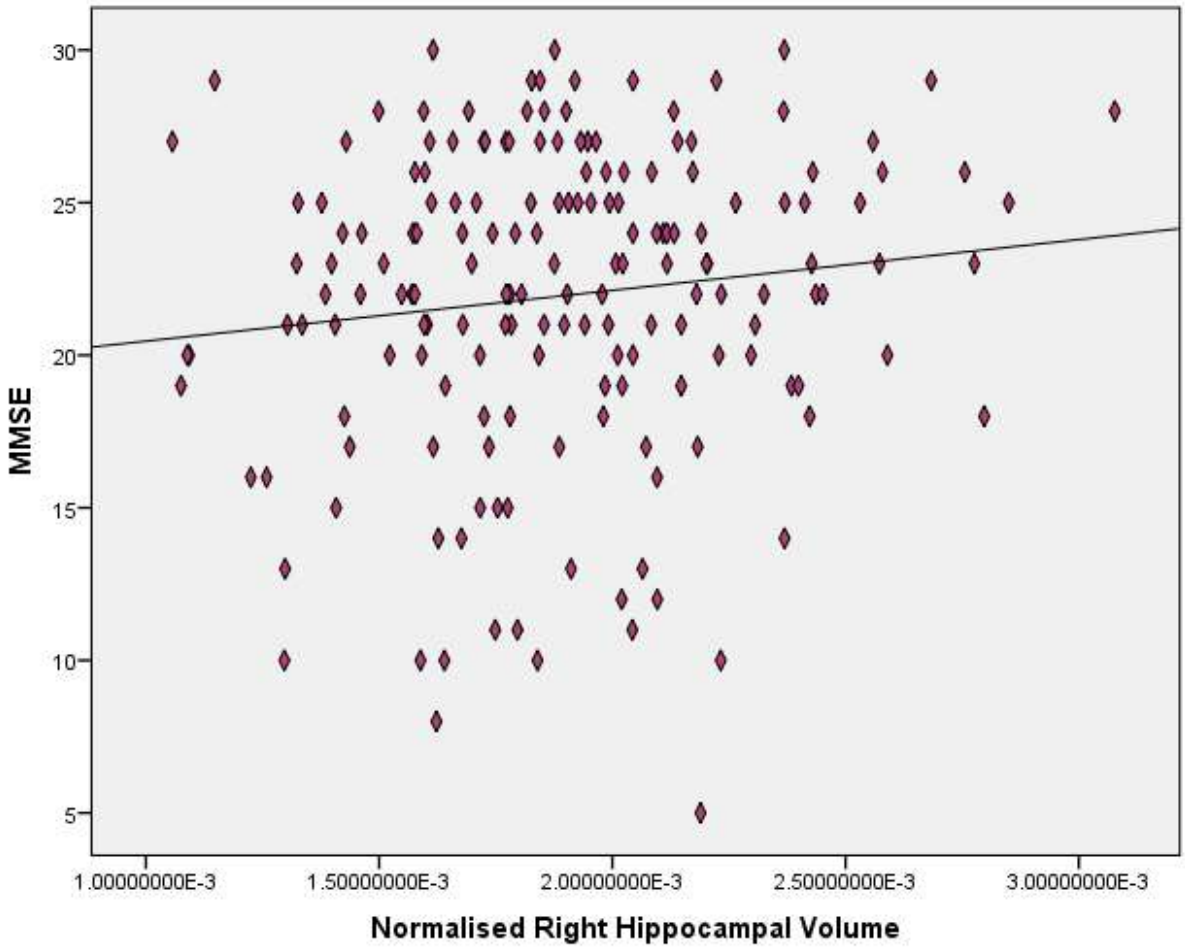


*Table 3-5– Correlation between MMSE score and Left and Right normalised hippocampal volumes. * denotes significant correlation at the p < 0.05 level.*

Disease Group	Average Left normalised HC volume	R – Correlation	P - value	Average Right normalised HC volume	R – correlation	P- value
Alzheimer's Disease	.00185	.224	.003*	.00189	.150	.048*
Mild Cognitive Impairment	.00212	.160	.231	.00217	.193	.146
Vascular Dementia	.00204	-.271	.156	.00208	-.133	.490
Mixed Dementia	.00188	.060	.679	.00184	.145	.316
Unspecified Dementia	.00197	-.141	.500	.00200	-.016	.939
Other Dementia	.00204	-.343	.332	.00217	.219	.554

3.4 DISCUSSION

In this study, we have successfully linked a large cohort of memory clinic patient's scans with their EHRs. This is, as far as we are aware, the first time that EHRs have been linked with fully automated analysis of regional MRI volumes and paves the way for further research studies. MMSE score was positively correlated with hippocampal volume in AD patients, as expected.

3.4.1 Hippocampal Volume and MMSE score

There have been several studies examining the relationship of hippocampal volume and cognitive functioning in healthy controls, and AD and MCI patients, and most have found the same positive correlation between hippocampal volume and various cognitive measures (Arlt et al., 2013; Mungas et al., 2002; Peng et al., 2015; Ridha et al., 2008; Sencakova et al., 2001; Yavuz et al., 2007). There is also evidence of correlation between other areas that are vulnerable to atrophy in AD, such as ventricular

enlargement or global atrophy rate (Ridha et al., 2008), however these are less explored and therefore hippocampal volume was chosen for this study.

3.4.1.1 Gender Differences in Normalised Hippocampal Volumes

It is well documented that there are gender differences between head size and brain volumes (Gur et al., 1999). Findings have shown females have larger normalised hippocampal volumes than men, despite having smaller raw volumes (Filipek, Richelme, Kennedy, & Caviness, 1994; Maller, Réglade-Meslin, Anstey, & Sachdev, 2006; Ystad et al., 2009). As this finding has been well documented, it was not an unexpected result in the current study.

Method of subcortical volume normalisation has been shown to influence gender differences (Nordenskjöld et al., 2015), and therefore method of volume normalisation should be taken into consideration when reviewing any study results. Normalisation methods, and subsequent potential confounds are further discussed in *section 3.4.2.2*.

3.4.1.2 Correlation between Hippocampal Volume and MMSE score

One study be Peng and Colleagues found baseline hippocampal volumes positive correlated with MMSE in both AD and MCI patients. Several studies have found that hippocampal volume is positively correlated with cognitive measures in MCI patients (Arlt et al., 2013; Peng et al., 2015), however these studies were only using amnesic MCI patients, whereas our memory clinic cohort did not only include patients with amnesic MCI, but any type of MCI.

Interestingly, while many studies have found this positive correlation between hippocampal volume and MMSE or other cognitive and memory measures, some found this relationship dissipates when looking at change in hippocampal volume or atrophy rate and either baseline cognitive measures or change in score (Ridha et al., 2008). This is most likely due to the lack of a linear relationship between change in hippocampal volume and MMSE score, or the lack of sensitivity in a MMSE (Mitchell, 2009).

Additionally, several studies have found unique relationships between hippocampal volume, MMSE score, and depression (Sawyer et al., 2012; Steffens et al., 2002). The patients in this memory clinic cohort did not have any depression measures, such as the Geriatric Depression Scale, to use in the analysis but it would be interesting to add such measures into a regression model in the future.

While the difference in correlation between hippocampal volume and MMSE is different by diagnosis, this finding could be expected. Hippocampal volume is seen to be smaller in VaD patients compared to normal controls, however it was also found to be significantly larger than AD patients (Kim et al., 2015). This lack of correlation between hippocampal volume and MMSE in VaD and Mixed Dementia patients that was seen in AD and MCI patients has also been observed previously (Mungas et al., 2002). VaD does not have the same clear neuropathology that seems to centralise in the MTL and hippocampus (O'Brien & Thomas, 2015a). It has previously been found that hippocampal volume is related to baseline cognition in cases without lacunes, an indication of cerebral vessel disease, white matter damage and VaD, but not those with lacunes (Mungas et al., 2002). Taken together, these findings could suggest diagnosis may be a significant mediating factor in the relationship between MMSE score and hippocampal volume, however this would need to be formally tested with a regression analysis to examine the interaction before drawing conclusions from the results presented here.

3.4.1.2.1 Correlation between Left versus Right Hippocampal Volume and MMSE score

There is substantial literature that right - left hippocampal asymmetry exists in healthy controls, pathological brains, and subjects with memory complaints (Geroldi et al., 2000; Pedraza, Bowers, & Gilmore, 2004; van der Flier et al., 2004). Similar to the current study, Peng and Colleagues found smaller left hippocampal volumes compared to right hippocampal volumes in subjects (Peng et al., 2015). This left right asymmetry was found to increase in conjunction with cognitive decline (Wolf et al., 2001). Rate of atrophy in the left hippocampus has been shown to correlate with performance on

MMSE, and change in MMSE score (Arlt et al., 2013). Lastly, there is evidence that the left hippocampus has more diagnostic accuracy than right hippocampal volume in AD (Slavin, Sandstrom, Tran, Doraiswamy, & Petrella, 2007). While the findings described in this study suggest there is a hippocampal asymmetry, as there was a higher correlation between left hippocampal volume and MMSE score in AD patients that was found, this was purely exploratory as no formal interaction was tested. This should however be taken into consideration into future, more in-depth studies, looking at mediating factors of the relationship between MMSE score and hippocampal volume.

3.4.2 Limitations

3.4.2.1 Electronic Health Records

The majority of the limitations of this study are related to the current state of use of EHRs in research and clinical practices. Many times, especially in the mental health fields, patient information is recorded in the form of free-text and not structured subfields. In turn, the quality of information recorded is heavily based on the clinician inputting it, and therefore recorded data may be incomplete (Perera et al., 2016). For example, our study had a total of 117 participants that had no diagnosis listed, this figure may be comprised of both people who did not receive a diagnosis at this time (but may later go on to receive one), people who were discharged before diagnosis, and those who potentially had a diagnosis but it was missing from their EHR. Another study found while EHRs lead to greater identification of suitable cases for research use, it also produced more missing fields (Newgard, Zive, Jui, Weathers, & Daya, 2012). This also creates the need for free-text searchers and algorithms to allow researchers to find relevant data, which can take a substantial amount of time to develop. While this was not directly an issue for the current study because CRIS has such systems in place (Perera et al., 2016; Stewart et al., 2009) it could make wider EHR research harder to implement. Majority of the limitations of EHR use lies

in implementation, because systems sufficient to handle research are not yet in place, however these should be considered short term as they would be alleviated with sustained use.

Another extremely important matter about the use of EHRs in research is the privacy concerns. There is the fear of stigmatization against those with mental health issues, making confidentiality one of the most important parts of EHR recording (Fernandes et al., 2013). The CRIS system has a complex security structure that removes any identifying information for patients, and furthermore only allows researchers to access such information within the SLaM firewall (Fernandes et al., 2013; Perera et al., 2016; Stewart et al., 2009). There is still concern whether or not anonymization of patient data is enough to keep information confidential (Rothstein, 2010). Reidentifcation of participants is possible with a combination of multiple databases, however this is predominantly an issue when data is allowed to be taken off site.

3.4.2.2 Hippocampal Volume Normalisation

Here, we have normalised hippocampal volumes by using a ratio of hippocampal volume divided by total intracranial volume. While this procedure has been used extensively, and has been cited as one of the most commonly used methods (Goldstein et al., 1999; O'Brien et al., 2011; Seidman et al., 1999), there are some concerns that this may not be the best way to normalise brain volumes as head size and subcortical volumes may not be related linearly (Barnes et al., 2010; Nordenskjöld et al., 2015; Voevodskaya et al., 2014).

Other approaches include regression and residual approaches (C. R. Jack et al., 1989; O'Brien et al., 2011; Voevodskaya et al., 2014). The regression approach uses the total ICV as a covariate in the regression model, while the residual model uses a linear regression between the volume of interest and total ICV to predict the adjusted volume of interest (C. R. Jack et al., 1989; Nordenskjöld et al., 2015). There is evidence that while systematic errors in ICV can affect means based on this proportion method,

the statistical power associated with group differences remains unchanged (Sanfilipo, Benedict, Zivadinov, & Bakshi, 2004). The regression and residual approaches have the flexibility to model a quadratic effect of ICV, allowing for non-linear relationships between regions of interest and head size (O'Brien et al., 2011). More specifically, the regression approach allows interactions to be modelled as well, for example if there was a relationship between total ICV and diagnostic group) (O'Brien et al., 2011; Sanfilipo et al., 2004). All of the methods listed can create biases under various scenarios, and each method can provide different results (Arndt et al., 1991; Barnes et al., 2010; Malone et al., 2015; O'Brien et al., 2011), which is important to remember when interpreting the results reported here. Additionally, there is some evidence that subcortical volumes do not need to be normalised when predicting AD (Zhou et al., 2014). In the future, it would be best to compare the three various correction methods to find the most suitable one for the current analysis.

3.4.2.3 The MMSE

While the MMSE is the most commonly used cognitive test in the diagnosis of AD and dementia (Arevalo-Rodriguez et al., 2015), there are over 20 brief (less than 20 minutes) cognitive tests used for people with suspected dementia that have diagnostic validity data. At least five of these have been validated for use in both primary care and specialist memory services (Velayudhan et al., 2014). The MMSE has shown to provide modest accuracy, however it is found to be best for ruling out dementia when identifying potential MCI in a secondary specialist centre (Mitchell, 2009). The Addenbrooke's Cognitive Examination III (ACE-III) has been shown to be a valid test for distinguishing dementia disorders, such as AD and Fronto-temporal Lobe Dementia (FTLD), and has better diagnostic accuracy than the MMSE (Hsieh, Schubert, Hoon, Mioshi, & Hodges, 2013; Larner & Mitchell, 2014).

The MMSE has several limitations such as a floor-effect in patients with advanced dementia, those with little formal education, and non-English speaking groups (Schultz-Larsen, Kreiner, & Lomholt, 2007;

Vertesi et al., 2001), and ceiling effects in those with very mild dementia (Simard, 1998). Additionally, 12% of variance in MMSE scores can be contributed to age and education alone, indicating other tests may be more sensitive to cognitive changes due to AD.

Because of the nature of the memory clinic cohort, many subjects may be assessed whilst only having slight memory impairment, and may be subject to the ceiling effects of the MMSE previously mentioned. This correlation analysis does not account for this ceiling effect of the MMSE, and this should be considered when interpreting the results. In the future, modelling techniques such as specific forms of multiple regression may be useful in taking these ceiling effects into consideration (Matthew McBee, 2010).

In our cohort, the MMSE was the only widely used cognitive examination. Even then, only slightly less than 60% of memory clinic patients had an MMSE score in their EHR, illustrating the difficulty in finding a widely used cognitive test in memory clinics. It would be interesting to work towards the standardisation of memory clinic neuropsychological batteries and cognitive examinations, to more deeply explore the relationship of brain structure and cognitive functioning in this type of cohort.

3.4.3 Future Directions

While this study concentrated on the feasibility between linking clinical EHRs with MRI data, the possibilities extend far past that. We were able to take a large clinical sample of over 500 patients, and link their analysed MRI scans with the hospital's repository. Neuroimaging plays a prominent role in the diagnosis of AD and dementia, however, it is not sufficient on its own and must be used in conjunction with the other core clinical criteria for diagnosis (G. M. McKhann et al., 2011). The current guidelines for dementia diagnoses state that biomarkers, including those that are imaging based, are in need of further study and validation before they can be used in the core clinical criteria. This study is one of first steps in validating such methods in a clinical setting instead of using a research cohort.

Our next plan is to extend this study to use more advanced analysis, such as machine learning techniques that have demonstrated good classification of AD and MCI individuals versus healthy controls using other brain regions of interest and cortical measures, and have potential in predicting which MCI patients will go on to develop AD (Aguilar et al., 2013a; Khan et al., 2015; Westman, Cavallin, Muehlboeck, et al., 2011b; Westman, Simmons, Zhang, et al., 2011). There are several potential confounds that lie with using a research based cohort as they are not generally representative on the general older population (Sperling et al., 2011) that may be alleviated by using this clinical sample. If such techniques are validated, we can move forward to potentially combine all available health data (such as aforementioned CSF measures) and create more comprehensive indices (Spulber et al., 2013; Westman et al., 2012) that may aid clinicians. If such biomarkers do become validated, having a linkage system in place will allow clinicians to run automated volumetric analyses and link them to other health records with ease, ultimately streamlining the entire diagnostic process.

Another advantage of aggregating health information, for both researchers and clinicians, in one centralized location is the ability to obtain more information. Specifically, in AD there is evidence that combining CSF measures with volumetric data is more effective and classifying AD and MCI versus healthy individuals than either measure on their own (Westman et al., 2012). Because AD is such a complex disease, there is much to be learned about less validated biomarkers. EHRs provide the opportunity to include genetic markers such as APOE status (Mahley & Rall, 2000), other blood based bio-markers that potentially indicate dementia due to AD, or even other neuroimaging data such as PET and resting-state fMRI. Most biomarkers have not been validated against one-another, and therefore the research on the use of combinations of biomarkers is fairly limited (Albert et al., 2011). For example, ADNI is an impressive cohort with over 800 subjects with neuroimaging data (www.adni-info.org) but only roughly half of the sample has CSF measurements. EHRs can help bridge this gap and create a database with a more complete dataset for individuals.

Numerous studies have been made possible due to the new case registrar system in place at SLaM. CRIS has provided researchers with a large repository of data that allows for extra information not normally obtained through traditional research cohorts. The potential uses of such a linkage go far beyond AD and dementia. In recent years, there has been a surge in the use of neuroimaging data in disease diagnosis, prognosis and stratification (Arbabshirani, Plis, Sui, & Calhoun, 2016). Other psychiatric and neurological disorders such as schizophrenia, depressive disorders, Autism Spectrum Disorder, and ADHD may also benefit from congregating neuroimaging data with electronic health records from both the perspective of clinician use and research use.

The possibilities extend far past psychiatric disorders and neuroimaging. Here we have demonstrated some of the useful information that can be extracted from structural neuroimaging, but there is also potential for use of other types of structural imaging such as lesion load in white matter diseases such as multiple sclerosis or stroke, and functional neuroimaging such as function MRI, PET, spectroscopy or electroencephalography (EEG). Because clinical imaging does not stop at the brain there is a variety of opportunity to link imaging data to further research other disease such as cancers and other injuries. This is a proof of principal to integrate any type of imaging with EHRs; further disciplines such as oncology, pathology, cardiology, and countless others can benefit from the research potential that this study poses. While here we have connected data extracted from patient scans, there may be opportunity in the future to link actual scans to allow researchers more flexibility with what specific analyses they wish to carry out.

Furthermore, this implementation of anonymized EHRs provide researchers with a platform to identify patients that may be interested in participating in future studies. This has begun to be implemented in the CRIS system already (Callard et al., 2014), however may benefit from added information due to the new linkages we have employed in this study.

3.5 CONCLUSION

This study demonstrated that connecting electronic health data with clinical neuroimaging data is indeed possible, and could benefit both future research endeavours and diagnostic techniques. Furthermore, as expected MMSE and hippocampal volume are significantly positively correlated in patients with AD.

4 OPLS IN A MEMORY CLINIC COHORT

4.1 INTRODUCTION: MULTIVARIATE ANALYSIS IN DEMENTIA

Advents in both imaging techniques and image analysis have led to the development of ways to explore the large amount of data that can come from a single magnetic resonance imaging (MRI) scan. Because of the complexity and heterogeneity of Alzheimer's Disease (AD) pathology, it is unlikely that a single region will give comprehensive information about disease progression. This has prompted researchers to examine systematic changes in both structure and function of the brain, and other different biomarker modalities such as cerebrospinal fluid (CSF) and blood measures. Because of the large amount of information that comes from these examinations, more complex multivariate analyses and machine learning techniques have developed to analyse a large amount of data simultaneously, exposing inherent patterns in the data. As a result, it is possible to determine patterns that respond to a specific group, determine what variables are responsible for the separation, and ultimately make predictive models. Most commonly, these algorithms are able to distinguish AD patients from healthy control subjects. Furthermore, these techniques have also been used to predict conversion from Mild Cognitive Impairment (MCI) to AD, reiterating the importance and potential use for detecting AD at the prodromal stage, before any kind of clinical indications.

4.1.1 Types of Multivariate Analyses in Dementia

Multivariate analysis techniques provide analysis methods to measure multiple quantitative variables at once, giving a more comprehensive outlook. This kind of test can be used to support clinical diagnoses, and may provide more detailed information due to its quantitative nature, rather than current visual assessments and rating scales (Westman, Cavallin, Muehlboeck, et al., 2011b). In multivariate analysis techniques, one simultaneous test is performed on all variables at once, providing an opportunity to

view intrinsic patterns in the data. This allows for a number of correlations between pairs of MRI measures to be considered which is not possible in univariate modelling. Because it is one test, it circumvents the need for multiple comparisons correction. Since there are quite a large number of biomarkers that are related to dementia and Alzheimer's disease specifically (medial temporal lobe (MTL) volumes and CSF measures such as p-tau, t-tau, and Aβ-42 for example) a multivariate analysis technique is more appropriate to ensure all relevant variables are considered (Westman, Simmons, Zhang, et al., 2011; Westman et al., 2012). Multivariate analysis can take a large set of data, including imaging and the aforementioned measures, and summarise it into one score. This could provide easier interpretability for clinicians, and could aid diagnostic processes in the future.

There are a variety of supervised classifiers used for model prediction containing MRI data. Supervised classifiers use previous knowledge about group characteristics to learn from a training set of data. Following training, the classifier is then able to label new, previously unseen data. Support vector machines (SVM) are the most commonly used classifier algorithm (Falahati, Westman, & Simmons, 2014), but others such as orthogonal projection to latent structures (OPLS) (Trygg & Wold, 2002), linear discrimination analysis (LDA), artificial neural networks (ANN), decision trees (DT) and ensemble or regression-based methods. None of these techniques were developed specifically for neuroimaging data, however they all show promising classification results

After deciding on a classifier method and algorithm, the subset of variables that will be used as input data must be chosen. Features can come from a variety of data sources, including both structural and functional imaging, and aim to provide the most relevant information on disease patterns. Currently, most attention is focused on structural imaging and features can range anywhere from single voxels to broader ROIs or structures, to whole brain characteristics. Most commonly, volumetric and thickness measurements of both cortical and subcortical regions are used (Simmons et al., 2011; Westman, Aguilar, Muehlboeck, & Simmons, 2013). Feature extraction is a crucial part of the method as analysis

techniques can directly affect classification performance, therefore segmentation techniques must be accurate and robust (Cuingnet et al., 2011).

Following feature extraction, the most relevant features must be selected for use in the classification analysis. With the new advents in neuroimaging, a myriad of information can come from a single image. Because of the high dimensionality of the data, computing all the information can be difficult. Large amounts of data or features can create over-fitted models, where the classifier is too closely fit for a small number of subjects. Additionally, adding irrelevant features in the classification model can introduce noise and diminish accuracy. This can be combated by using feature selection, where only the most relevant data to the disease are included in the model. In addition to creating a more accurate model, feature selection can reduce computational power and time needed, and may make the final result less complex and easier to interpret.

Several methods can be used to evaluate the classifiers. The first method is cross-validation (CV), and can be done in several different ways. Part of the data set is used as a training set and the rest is used as an unseen, unclassified dataset to test the algorithm. This process of taking a portion of the data out and using the rest as the test set is repeated several times (Westman, Simmons, Zhang, et al., 2011). CV is well-suited for small datasets when it is not possible to leave out a large portion of the data exclusively for training. If samples sizes are large enough, a training set can be created using a set of the data and CV is used to create the model. Following model creation, the rest of the data is used as a test set.

Comparing different methods of multivariate analyses can be difficult because there are a large variety of variables that may influence accuracy. Aside from methodological factors such as extraction methods, feature selection, classification and validation techniques, there can be differences due to cohort properties such as demographics, number of subjects, and image quality.

4.1.2 OPLS in Dementia Imaging Studies: Research Cohorts

There has been extensive review of multivariate data analysis and machine learning techniques in AD. The techniques mentioned earlier, SVM, OPLS, and LDA, have all been shown to provide accuracy over or just below 90% in distinguishing structural MRI of AD patients versus healthy controls (Falahati, Westman, & Simmons, 2014). The consensus is that a diagnostic biomarker must achieve a sensitivity of at least 80%, and distinguish between both healthy controls and other types of dementia, to be clinically useful ("Consensus Report of the Working Group on," 1998; Hampel, Frank, et al., 2010; Hampel, Lista, & Khachaturian, 2012).

There is some evidence that OPLS performs better than other methods such as ANN and DT, and was therefore chosen for this specific study (Aguilar et al., 2013b). OPLS has been used extensively in research cohorts, including combining multiple cohorts such as AddNeuroMed and the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Westman, Simmons, Muehlboeck, et al., 2011).

In terms of potential clinical use, OPLS has proven to be better at distinguishing AD patients than visual rating scales (VRS) alone (Westman, Cavallin, Muehlboeck, et al., 2011). It is able to distinguish between MCI patients that remain stable and those who go on to convert to AD, proving it may have clinical utility (Spulber et al., 2013). Disease severity indices have been created through OPLS analyses, and are even sensitive to people with subjective memory decline (Daniel Ferreira, Falahati, et al., 2017; Spulber et al., 2013). Furthermore, OPLS can use more than structural imaging measures alone. Combining other measures such as CSF biomarkers may improve classification and be promising for clinical use (Westman, Wahlund, Foy, et al., 2011; Westman et al., 2012).

4.1.3 Rationale and Hypotheses

Today, structural MRI is most often standard in routine memory clinic diagnostics. Because of this, in combination with the fact that structural MRI multivariate image analysis has proven to provide good

sensitivity and specificity in research cohorts, we have extended the application of OPLS to a clinical cohort. Research cohorts have very strict inclusion and exclusion criteria, and therefore eliminates the natural heterogeneity that is found in the population. To have clinically efficacy, multivariate analysis tools must be useful on clinical cohorts, that do not have such rigid criteria and may include patients with one or more comorbidities. Additionally, OPLS models are trained on AD and healthy control data, and there are few studies looking at multivariate analysis techniques for distinguishing different types of dementia, one of the main challenges clinicians face. The goal is to test the applicability to memory clinics, and examine the diagnostic value of this tool. While classification is expected to be less accurate than shown in research cohorts, the model should show decent classification sensitivity and accuracy in classifying AD patients as having an AD-like brain. Because of AD-like pathology in mixed dementia (MD) patients, it is expected that they will also be highly classified as AD-like. Those diagnosed with MCI are expected to have a fairly mixed classification result, as this may reflect those who go on to develop AD versus those who revert back to normal cognition or go on to develop another form of dementia. Other dementias, such as Vascular Dementia (VaD), are not expected to have the same classification profiles, and may be more classified as control-like.

4.2 METHODS

4.2.1 Participants

4.2.1.1 ADNI / ADDNEUROMED Training Datasets

Our training dataset included a total of 637 participants, 402 from the ADNI dataset and 235 from the AddNeuroMed dataset (Lovestone et al., 2009; Mueller et al., 2005).

4.2.1.1.1 Inclusion Criteria

Both the ADNI and AddNeuroMed cohorts have similar recruitment methods and inclusion criteria (R C. Petersen et al., 2010; Simmons et al., 2011). Dementia was diagnosed following the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (American Psychiatric Association, 1994), while probable AD was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (G. McKhann et al., 1984), as well as a clinical dementia rating (CDR) score of 0.5 or above. MRI imaging was not taken into consideration during diagnosis. To be qualified as a healthy control (HCS), participants needed an MMSE score between 24 and 30, a CDR score of 0, and a Geriatric Depression Scale (GDS) score of less than 5. Participants, from any of the groups were not permitted to have significant neurological or psychiatric illnesses, or any significant unstable systemic illness or organ failure. Additionally, no history of alcohol or substance abuse or dependence was required for all three groups.

4.2.1.1.2 Demographics

The training set included 297 diagnosed AD participants, and 340 healthy controls. There were 337 females and 300 males, with an age range of 52-90 years (Table 4-2).

4.2.1.2 Memory Clinic Cohort

The memory clinic cohort was comprised of patients from the South London and Maudsley NHS trust (SLaM), who had been referred to a memory clinic after experiencing memory difficulties. The demographic information for the memory clinic cohort and inclusion criteria can be found in *Chapter 2: The Biomedical Research Centre Memory Clinic Cohort, section 2.2.1*. For this study, we used a total of 668 participants whose scans passed quality control checks as described in *Chapter 2* (Table 4-3).

4.2.2 Imaging

4.2.2.1 MRI Acquisition

4.2.2.1.1 ADNI/AddNeuroMed Training Set

The AddNeuroMed study was designed specifically to be comparable with ADNI, and therefore have the same acquisition parameters (Clifford R. Jack, Bernstein, et al., 2008; Clifford R. Jack et al., 2015; Simmons et al., 2011). Both protocols include a high resolution sagittal 3D T1-weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE) volume and axial proton density/T2-weighted fast spin echo images. MPRAGE images were acquired with 1.1×1.1×1.2 mm^3 voxel size. All images needed full brain and skull coverage, and were further analysed for full quality control measures as described previously (Lovestone et al., 2009; Simmons et al., 2011).

4.2.2.1.2 Memory Clinic Cohort

The image acquisition and quality control procedures for the BRCMEM cohort was based on ADNI and AddNeuroMed parameters, and is described in detail in *Chapter 2: The BRCMEM Cohort, section 2.2.2*.

4.2.2.2 Tissue Segmentation

The T1 images were analysed with the FREESURFER pipeline version 5.3.0 (http://surfer.nmr.mgh.harvard.edu/) to produce regional cortical thickness and subcortical volume measures. The pipeline includes removal of non-brain tissue using a hybrid watershed/surface deformation procedure (F. Ségonne et al., 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep grey matter volumetric structures (Bruce Fischl et al., 2002; Bruce Fischl, Salat, et al., 2004; F. Ségonne et al., 2004) intensity normalisation (Sled et al., 1998), tessellation of the grey matter white matter boundary, automated topology correction (B. Fischl et al., 2001; Florent Ségonne et al., 2007), and surface deformation following intensity gradients to optimally place the grey/white and grey/cerebrospinal fluid borders at the location where the greatest shift in intensity

defines the transition to the other tissue class (A. M. Dale et al., 1999; Anders M. Dale & Sereno, 1993; B. Fischl & Dale, 2000). Once the cortical models are complete, registration to a spherical atlas takes place which utilises individual cortical folding patterns to match cortical geometry across subjects (B. Fischl et al., 1999). This is followed by parcellation of the cerebral cortex into units based on gyral and sulcal structure (Desikan et al., 2006; Bruce Fischl, van der Kouwe, et al., 2004). The pipeline generated 68 cortical thickness (34 from each hemisphere) and 21 regional subcortical volumes (Table 4-1). This segmentation approach has been used for multivariate classification of Alzheimer's disease and healthy controls (Westman, Wahlund, Foy, et al., 2011), neuropsychological-image analysis (Yawu Liu et al., 2011; Yawu Liu, Paajanen, Zhang, et al., 2010), imaging-genetic analysis (Yawu Liu, Paajanen, Westman, Wahlund, et al., 2010; Yawu Liu, Paajanen, Westman, Zhang, et al., 2010) and biomarker discovery (Thambisetty et al., 2010).

Table 4-1 – *List of FREESURFER outputs, including all Cortical Thicknesses and Subcortical structures used in the OPLS analysis*

Cortical Thicknesses (both Right and Left)	Subcortical structures
Banks of superior temporal sulcus	Third ventricle
Caudal anterior cingulate	Fourth ventricle
Caudal middle frontal gyrus	Brainstem
Cuneus cortex	Corpus callosum anterior
Entorhinal cortex	Corpus callosum central
Fusiform gyrus	Corpus callosum midanterior
Inferior parietal cortex	Corpus callosum midposterior
Inferior temporal gyrus	Corpus callosum posterior
Isthmus of cingulate cortex	Cerbrospinal Fluid (CSF)
Lateral occipital cortex	Accumbens
Lateral orbitofrontal cortex	Amygdala
Lingual gyrus	Caudate
Medial orbitofrontal cortex	Cerebellum cortex
Middle temporal gyrus	Cerebellum white matter
Parahippocampal gyrus	Hippocampus
Paracentral sulcus	Inferior lateral ventricle
Frontal operculum	Putamen
Orbital operculum	Lateral ventricle
Triangular part of inferior frontal gyrus	Pallidum
Pericalcarine cortex	Thalamus proper
Postcentral gyrus	Ventral diencephalon (DC)
Posterior cingulate cortex	
Precentral gyrus	
Precuneus cortex	
Rostral anterior cingulate cortex	
Rostral middle frontal gyrus	
Superior frontal gyrus	
Superior parietal gyrus	
Superior temporal gyrus	
Supramarginal gyrus	
Frontal pole	
Temporal pole	
Transverse temporal cortex	
Insular	

4.2.2.2.1 Volume Normalisation

All subcortical volumes were normalised by dividing by each subject's intracranial volume (ICV), while leaving all cortical thickness measures in their raw form. This method has been used previously in OPLS analyses, and provides the best models (Westman et al., 2013).

4.2.3 OPLS Analysis

4.2.3.1 Preprocessing

To begin, data are preprocessed to centre the mean and scale to unit variance. Mean centring subtracts the variable average from the data, repositioning it about the origin. This serves to improve interpretability of the data later on. Because large variance variables are more likely to be prominent in the model than low variance variables, unit variance scaling is used to balance the data appropriately. In this technique, standard deviation of each variable is calculated, and then the inverse standard deviation is used as a scaling weight for each variable (Eriksson et al., 2006; Westman, Cavallin, Muehlboeck, et al., 2011b; Westman, Simmons, Zhang, et al., 2011; Westman et al., 2012). Finally, prior to OPLS analysis, all data was reviewed in a scatter plot of first and second PCA components, with a Hotelling's T2 elliptical range with 95% confidence intervals to ensure data was normally distributed and identify outliers (Iwashita, 1997).

4.2.3.1.1 Age Correction

There are global and regional brain changes that are thought to be related to healthy ageing in the absence of dementia. Because of this confound, these factors may negatively affect model performance (Dukart, Schroeter, Mueller, & Alzheimer's Disease Neuroimaging Initiative, 2011; Falahati et al., 2016). OPLS studies have shown excellent classification performance, even without performing age corrections (Simmons et al., 2011; Westman, Cavallin, Muehlboeck, et al., 2011b; Westman, Simmons, Muehlboeck, et al., 2011; Westman, Simmons, Zhang, et al., 2011; Westman et al., 2013, 2012). More recently, Falahati and colleagues demonstrated that age correction can improve both classification and prediction performance using a research-based cohort (Falahati et al., 2016). For this study, both age corrected and the standard method without age correction were used and then later compared.

To carry out the age correction, a linear detrending algorithm based on age-related changes was used. This algorithm fits a generalized linear model (GLM) to the MRI variables and age in the control group, and models any age-related changes as a linear drift. This linear drift is expressed as the regression coefficient of the GLM model, and serves to remove age related changes in all participants, namely those in the memory clinic cohort. This model was based on an age-related linear decrease in global grey matter volume in healthy individuals (Good et al., 2001). The correction measures the age-related changes in the control group, and remove these age-related changes to allow better analysis of only disease-related changes in the AD group. In the current study, the linear detrending algorithm was based on the healthy controls in the ADNI/AddNeuroMed training set, and then applied to both the AD subjects in the training set (to ensure appropriate modelling) and the BRCMEM memory clinic test set.

4.2.3.2 OPLS

OPLS is a supervised multivariate data analysis method that has been extensively used locally because of its high, cross-validated sensitivity, specificity, and likelihood ratios, indicating a good diagnostic tool (Simmons et al., 2011; Westman, Cavallin, Muehlboeck, et al., 2011b; Westman, Simmons, Muehlboeck, et al., 2011; Westman, Simmons, Zhang, et al., 2011; Westman et al., 2013, 2012). OPLS tries to maximise covariance between dependent and independent variables through the inherent relationship between latent variables. OPLS is a method based on partial least squares to latent structures (PLS) and orthogonal signal corrections (OSC) (Trygg & Wold, 2002). PLS utilises attributes from and combines both principal component analysis and multiple linear regression. This method has been used to analyse MR data successfully in the past (Levine et al., 2008; McIntosh & Lobaugh, 2004; Westman et al., 2009). PLS models the relationship between two sets of variables by fitting and aligning two models, one for independent variables and another for dependent variables simultaneously. Ultimately, the PLS aims to model both independent and dependent variables, and predict the dependent variables from the independent variables. PLS can mathematically be described as:

$$X = 1 * \bar{x'} + T * P' + E$$

Equation 4-1 - *Description of X variables in PLS model*

$$Y = 1 * \bar{y'} + U * C' + F$$

Equation 4-2 – *Description if Y variables in PLS model*

In this equation, $1 * \bar{x'}$ and $1 * \bar{y'}$ represent the variable averages (X being independent variables and Y being dependent variables) calculated in the preprocessing step of mean centring. T and U represent matrices related to the observations, describing their similarity or dissimilarity depending on the given model. Matrices P' and C', X-loading and Y-loading respectively, contain information about the variables. Finally, the E and F terms describe the residual matrices that contain the noise, or unmodeled data (Eriksson et al., 2006).

OPLS takes the PLS methodology, and combines it with OSC. The purpose of the orthogonal correction methods is to remove the variation in the independent variable matrix that is not correlated to the dependent variable matrix. This method allows for the separation of the independent variable matrix into two blocks based on the data in the Y or dependent variable matrix: one of structured or correlated variation and the other uncorrelated variation that is classified as orthogonal to the dependent variable matrix. There are three criteria these orthogonal correction methods poses on the component including: 1) the component must address large systemic variations in X 2) the component must be predictive by X, to apply to future data and 3) the orthogonal component must be orthogonal to Y. The first two criteria are easily computed with by running a PCA of X, while the third is more difficult but can be accomplished using the aforementioned OSC (Trygg & Wold, 2002; Westman et al., 2012).

OPLS and PLS are very similar, and give the same predictive accuracy. However, OPLS has an advantage where the model created to compare groups is rotated, meaning the information related to class separation is found in the predictive, or first, component of the model. If there are other orthogonal

components, they relate to variation in the data not connected to class separation. This part of the process makes data interpretation significantly easier (Westman, Simmons, Zhang, et al., 2011; Wiklund et al., 2008).

The OPLS method can also be described mathematically as:

$$X = T_P P_P^T + T_O P_O^T + E$$

Equation 4-3 – *Description of X variables in OPLS model*

$$Y = T_P C_P^T + F$$

Equation 4-4 – *Description of Y variables in OPLS model*

Here, $T_P P_P^T$ represents the correlated variation (or the Y-predictive block) and $T_O P_O^T$ represents the uncorrelated variation (or Y-orthogonal block).

OPLS analysis results is characterised by a $Q^2(Y)$ value that describes the predictability of the model, or the significance for separating groups (Eriksson, Byrne, Johansson, Trygg, & Vikström, 2013). $Q^2(Y)$ the portion of total variation in expected class values that can be predicted by CV. $Q^2(Y)$ values > 0.05 are regarded as significant (Eriksson et al., 2006). This can be described as:

$$Q^2(Y) = 1 - (PRESS - SSY)$$

Equation 4-5 – *Predictability of model*

The predicted residual sum of squares (PRESS) can be described as:

$$PRESS = \sum (Y_{actual} - Y_{predicted})^2$$

Equation 4-6 – *Predicted Residual Sum of Squares*

and SSY describes the total variation in the Y matrix after mean centering and variance scaling (Eriksson et al., 2006).

$Q^2(Y)$ is based on CV, and depicts how well the model can predict new data. CV is a statistical technique used to verify predictive models. This involves building a number of parallel models that differ from each other by leaving out a specified piece of the data set each time, which is then predicted by the respective model. Based on experimenter preference, a number is chosen for cross validation. In the instance of Westman et al. 2012, seven-fold cross validation was used, meaning $1/7^{th}$ of the data was removed for each cross validation round, and seven rounds were completed (each portion of data being left out only once) (Westman et al., 2012).

Additionally, there is an $R^2(Y)$ parameter that describes the goodness of fit of the model. $R^2(Y)$ describes the fraction of the variation in the training components that is explained by the various components of the model (Eriksson et al., 2013), essentially describing how well the model fits the training set of data.

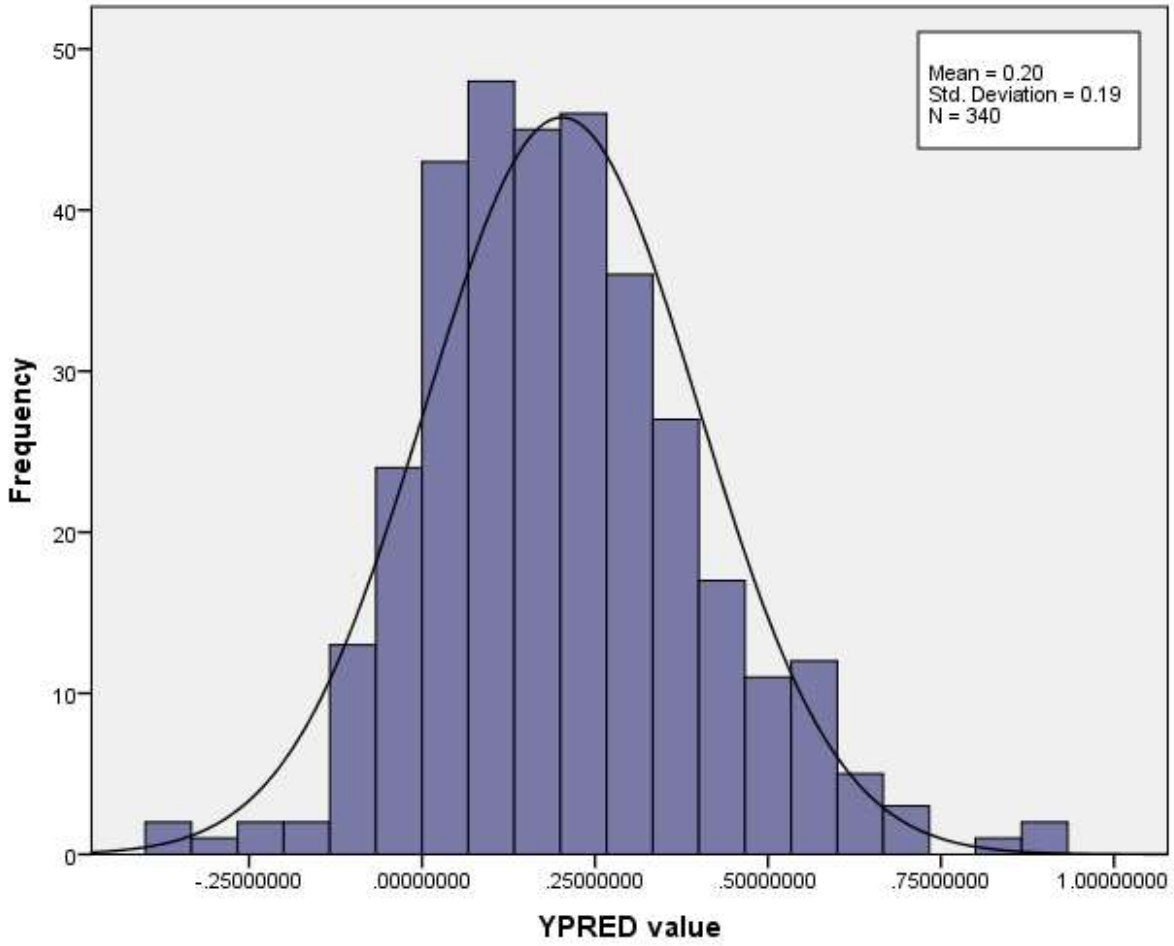
In the context of this study, the ADNI and AddNeuroMed data were used to create and train the model using 7-fold CV. The memory clinic data was then tested using this model created, and for each new subject a prediction value (ypred) was created based on the model.

4.2.3.2.1 OPLS Cut-off Values

The ypred, or AD Atrophy score, for a subject ranges from 0 to 1, whereas 0 is maximum likelihood for one group (controls), 1 is the maximum likelihood for the other group (AD), and 0.5 is considered the appropriate cut off value for accepting the observation as correctly predicted (Westman, Cavallin, Muehlboeck, et al., 2011b; Westman, Simmons, Zhang, et al., 2011; Westman et al., 2012).

Recent studies have explored using a different cut-off that is more representative of the inherent homogeneity of AD (Falahati et al., 2017). This second cut-off was calculated by taking the average AD Atrophy score for heathy controls, and adding one standard deviation. The new cut-off of 0.390 (average AD Atrophy score of controls = 0.20 + one standard deviation = 0.19) is based off a previous study that used deviation from healthy controls to define cognitive impairment. This study found that using one standard deviation from healthy controls had the highest predictive power for subsequent development of dementia (Busse, Hensel, Guhne, Angermeyer, & Riedel-Heller, 2006). This new cut-off was derived from the average uncorrected AD Atrophy scores of the healthy controls from the ADNI/AddNeuroMed Training set (Figure 4-1). Using corrected AD Atrophy scores, calculated from the age correction method described in *section 4.2.3.1.1*, revealed the same cut-off of 0.390 (average AD Atrophy score = 0.20 + one standard deviation = 0.19).

Figure 4-1 *– Histogram of age-uncorrected AD Atrophy score for healthy controls from ADNI/AddNeuroMed training set. Average AD Atrophy score = 0.20; Standard Deviation = 0.19 which created a new cut-off of 0.39*



4.2.3.2.2 Variable Importance in Group Separation

An additional feature of OPLS analysis is variables can be plotted according to their contribution to group separation (Figure 4-2). Variables are ordered according to their importance, and covariance is plotted on the y-axis. Jack-knifed confidence intervals are included to estimate bias and standard errors. Various sub-models from cross validation results are used to calculate standard error of different variables, and n are converted into confidence intervals via the t-distribution (Eriksson et al., 2006). Parameters with high covariance are more likely to have a significant impact on group separation than

variables with low covariance, and variables whose confidence intervals cross zero can be considered to have low reliability (Wiklund et al., 2008). The covariance is plotted along the y axis and can be described as:

$$Cov(t, X_i) = t^T X_i \,/\, (N - 1)$$

Equation 4-7 – *Covariance of given OPLS variable, denoting importance for group separation*

The transpose of the score vector t in the OPLS model is represent by t, i is the centered variable in the data matrix X, and N is the number of variables (Wiklund et al., 2008). A $Cov(t, X_i)$ a below zero in the plots represents measures that have lower values in AD subjects compared to CTL subjects, while those measures above zero indicate a higher value in AD subjects compared to CTL subjects in the model.

For this OPLS analysis, all 89 volumes and cortical thickness measures (34 right and 34 left cortical thicknesses, and 21 subcortical volumes) from the FREESURFER output were used. To perform this analysis, including mean centring and variance scaling described in *section 4.2.3.1*, SIMCA version 13.0.3 (Umetrics AB, Umea, Sweden) was used.

4.2.4 Statistical Analysis

All statistical analyses on the memory clinic were performed with SPSS 21 software package, while analyses done on the training data were completed with SPSS 24. Results were considered significant at the $P < 0.05$ level.

4.2.4.1 Group Differences

4.2.4.1.1 ADNI/AddNeuroMed Training Set

Differences between the groups (healthy controls and AD subjects) were calculated for age, MMSE score, and years of education using an analysis of variance (ANOVA). Differences between gender distribution between the groups was measured with a X^2 test.

4.2.4.1.2 Memory Clinic Cohort

Out of the 668 participants for our memory clinic, 508 had some form of diagnosis in their clinical health records. 135 people had no diagnosis listed, and 25 received no diagnosis (such as person with mental health complaints). Because of the wide array of diagnoses, patients were categorised into one of the following groups: AD, MCI, MD, VaD, unspecified dementia, other dementia (such as Parkinson's or dementia in Pick's disease), or other psychiatric disorder (anxiety, depression, PTSD, or others). A one-way ANOVA was carried out to calculate differences between diagnostic groups for age and MMSE score, while a X^2 test was used to analyse the differences in gender distribution between the groups.

4.2.4.2 OPLS Model Analysis

Sensitivity, specificity, accuracy, predictive value, receiver operating characteristic (ROC) curves, and likelihood ratios are all statistical tools useful for assessing whether or not a diagnostic test is good. These measures were calculated for each the age corrected and uncorrected models from the cross-validated prediction values of the OPLS models.

4.2.4.2.1 Sensitivity and Specificity

Sensitivity is defined as the true positive or recall rate. It measures the proportion of actual positives that are correctly identified as such, for example: those with diagnosed with AD being classified as having AD via the OPLS models. Specificity is the true negative rate, or the proportion of actual negatives that are correctly identified as not having the disease. In this example, specificity would be the number

of healthy controls correctly classified as healthy controls (D. G. Altman & Bland, 1994a). Accuracy, or more specifically classification accuracy is the percentage of total number of correct classifications, out of all of the classifications.

4.2.4.2.2 Predictive Values

The positive predictive value (PPV), often called precision, is the ratio of true positives over all subjects that were classified as positive. This is used to indicate the probability that a patient actually has AD if they are put in the AD group by the classification technique being measured. Negative predictive value (NPV) is the ratio of true negatives over all subjects classified as negative (both true and false negatives). Predictive values are not only intrinsic to the test, but also heavily depend on actual disease prevalence in the sample (D. G. Altman & Bland, 1994b).

4.2.4.2.3 Receiver Operating Curves

ROC curves plot the true positive rate, or sensitivity as a function of the false positive rate (100-specificity) for various cut off points of a given test. The area under the curve (AUC) is used as an indicator of the quality of separation, with a score of .5 being completely random predictions and 1.0 being perfect separation (Hanley & McNeil, 1983; Metz, 2006).

4.2.4.2.4 Likelihood Ratios

Likelihood ratios are used for assessing the value of preforming a diagnostic test or classification, and determining whether the result reflects the probability of having a given condition. Positive likelihood ratios are equal to the sensitivity / (1 – specificity), and negative likelihood ratios are equal to (1 – sensitivity) / specificity. A likelihood ratio of greater than one indicates the test result is associated with the disease, while a ratio of less than one is associated with absence of the disease. Tests that have likelihood ratios equal to one have little practical significance, the further a likelihood ratio is from one, the stronger the evidence for the presence, or absence, of a disease. (Deeks & Altman, 2004). Positive

likelihood ratios between five and ten, or negative likelihood ratios between 0.1 and 0.2 are said to give a moderate increase in diagnostic values and ratios higher than 10 or lower than 0.1 considerably increase the diagnostic value of a test (Qizilbash et al., 2002; Westman et al., 2012).

4.2.4.3 Correlation between MMSE and AD Atrophy score

To follow up on the previous chapter's (*Chapter 3: Correlation of MMSE Score and Hippocampal Volume in a Memory Clinic Cohort*) findings, correlations were calculated between each participant's AD Atrophy score (both age corrected and age uncorrected) and MMSE score using Pearson correlations.

4.3 RESULTS

4.3.1 Demographics

4.3.1.1 ADNI / ADDNEUROMED Training Datasets

The training set included 297 diagnosed AD participants, and 340 HCS. There were 337 females and 300 males, with an age range of 52-90 years (mean =75.30 ±6.34; HCS=74.99 ±5.71, AD=75.67 ±6.97). There was no difference between age in the two groups. Only 622 participants had MMSE score information, which significantly differed between the two groups; (HCS=29.09 ±1.09, AD=22.22 ±3.70; p<.001). Years of education was also significantly different between AD and controls (HCS=14.25 ±4.38, AD=12.04 ±4.87; p<.001) (Table 4-2).

Table 4-2 - *Demographics for the ADNI/AddNeuroMed Training Set. Age, MMSE, and Years of Education = Mean (Standard Deviation). Differences between groups were measured by ANOVA, except for gender which was measured with X^2. * denotes significance at p <.001.*

	Healthy Controls	AD	P-VALUE
Number	340	297	
Age	74.99 (±5.71)	75.68 (±6.97)	0.174
Gender (M/F)	168/172	132/165	0.241
MMSE	29.09 (±1.09)	22.22 (±3.70)	<0.001*
Years of Education	12.08 (±4.83)	14.25 (±4.38)	<0.001*

4.3.1.2 Memory Clinic Cohort

The memory clinic cohort consisted of 668 patients that had structural T1 scans that passed quality control to run volumetric analyses. The average age was 73.40 (±10.55), with 195 males, 288 females, and 185 participants missing gender on their EHR. A total of 483 patients out of the 668 had a valid MMSE score (average=23.54±4.95) (Table 4-3).

Table 4-3 – *Demographics for the Memory Clinic Cohort.*

	Memory Clinic
Number	668
Age	73.40 (±10.55)
Gender (M/F/Missing)	288/195/185
MMSE	23.54 (±4.95)

A full breakdown of group differences based on diagnoses for the sample can be found in Table 4-4. As expected, there were significant differences in age, MMSE score, and gender distribution across groups. Because of the abundance of information following post-hoc analyses, the full results table is included as Appendix 2.

Table 4-4 - *Diagnosis Breakdown for the Memory Clinic Cohort. Age and MMSE = Mean (Standard Deviation). Differences between groups were measured by ANOVA, except for gender which was measured with X^2. * denotes significance at p <.001.*

	AD	MCI	MD	VaD	Other Dem	Unspecified Dem	Other Psych	No Diagnosis	Diagnosis not listed	P-Value
Number	212	90	63	28	33	10	72	25	135	
Age	77.10 (±7.33)	74.96 (±7.35)	79.06 (±6.45)	78.57 (±7.88)	68.90 (±8.40)	72.67 (±7.70)	67.04 (±11.06)	73.64 (±8.56)	66.70 (±13.88)	< 0.001 *
Gender (M/F/Missing)	69/91/52	24/34/32	11/32/20	9/13/6	5/5/0	11/12/10	19/30/23	7/7/11	40/64/31	0.210
MMSE	22.14 (±2.88)	26.69 (±2.95)	21.98 (±4.66)	20.95 (±4.55)	20.00 (±6.83)	20.43 (±5.43)	23.96 (±5.22)	26.00 (±2.88)	25.63 (±3.89)	< 0.001 *

4.3.2 Training Model Assessment

4.3.2.1 Age Uncorrected Model

The OPLS model without using age correction gave a $Q^2(Y)=0.549$ and a $R^2(Y)=0.598$, which is in line with other studies and regarded as a good model (Westman et al., 2012). The variables used in the model are plotted based on their importance to group separations with their corresponding jack-knifed confidence intervals, and are also very similar to previous models (Figure 4-2)(Westman, Simmons, Zhang, et al., 2011; Westman et al., 2012). The training model's predictive value was calculated using 7-fold CV in SIMCA to determine AD Atrophy scores for each of the training model subjects. Using these values and the same 0.5 cut-off, sensitivity, specificity, accuracy, NPV, PPV, likelihood ratios, and AUC were then calculated for training model. A graphic representation of classification of each group can be seen in Figure 4-3, with the grey dashed line representing the 0.5 cut-off. The training model gave a sensitivity and specificity in line with other studies (sens=90.00%; spec=84.40%), and can be seen in Table 4-5 (Falahati et al., 2014; Westman, Cavallin, Muehlboeck, et al., 2011b; Westman, Simmons, Muehlboeck, et al., 2011; Westman et al., 2012).

Figure 4-2 – *Structural MRI measures of importance for the separation between AD and healthy controls in the age uncorrected model. Measures with high variance (each end) are more likely to have an impact on group separation. Structures with a negative covariance have a lower value in AD subjects, while structures with positive covariance have higher values in control subjects. Measures are listed with jack-knifed confidence intervals, and those that include zero have low reliability for distinguishing groups.*

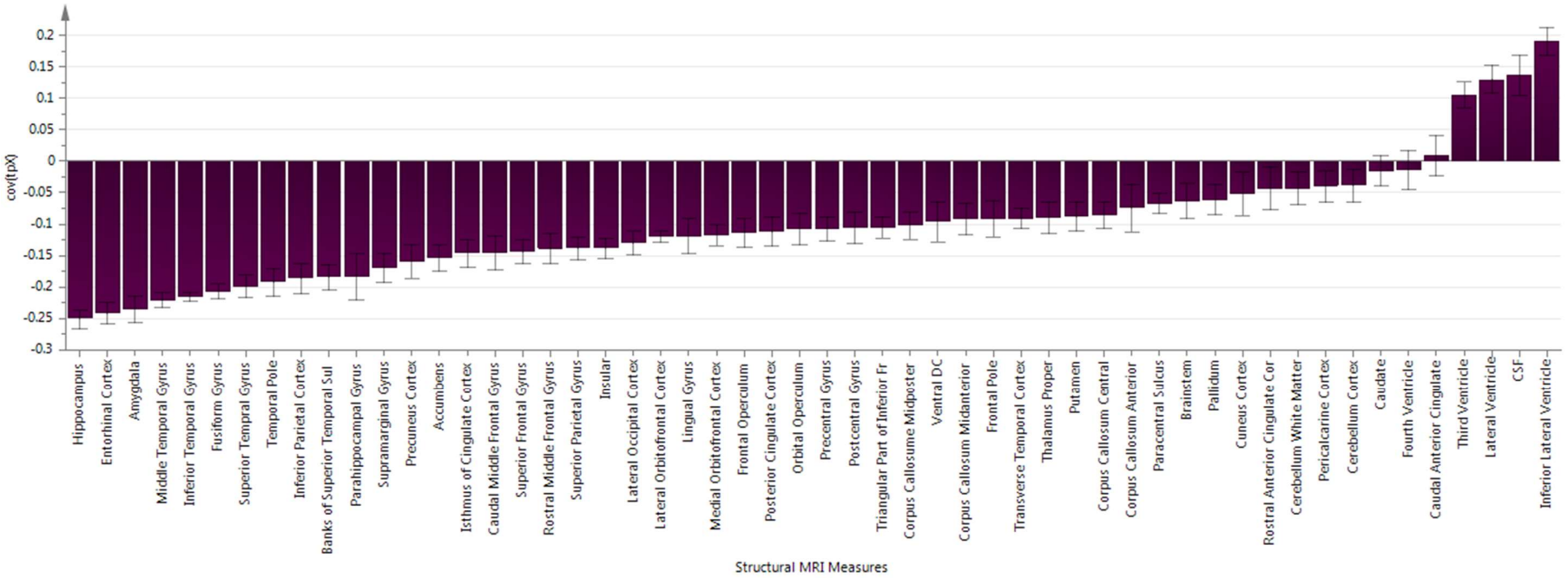


Figure 4-3 – *Class separation of the age uncorrected training model using 7-fold CV; grey dashed line represents 0.5 cut-off. Yellow triangles represent AD subjects and Magenta triangles represent healthy control subjects.*

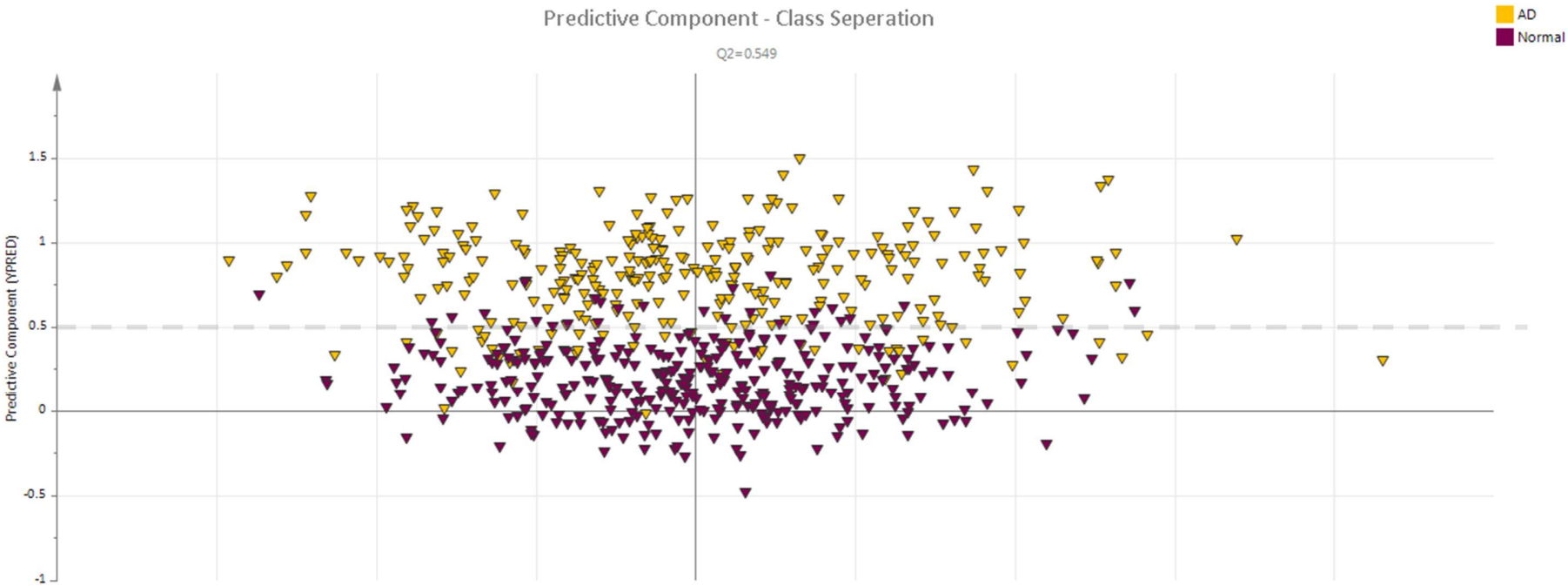


Table 4-5 – *Age Uncorrected Model Description*

Sensitivity	Specificity	Accuracy	LR+	LR -	PPV	NPV	AUC	Q^2	R^2
90.00%	84.40%	86.70%	5.77	0.12	90.10%	84.40%	0.937	0.549	0.598

4.3.2.2 Age Corrected Model

The OPLS model using the age correction method described in *section 4.2.3.1.1* gave a slightly improved of $Q^2(Y)=0.551$ and a $R^2(Y)=0.576$. Again, the variables used in the model are plotted based on their importance to group separations with their corresponding jack-knifed confidence intervals. While there are slight differences in variable importance, it is still the medial temporal lobe structures that are most important (Figure 4-4). The model's predictive value was again calculated using 7-fold CV in SIMCA to determine AD Atrophy scores for each of the training model subjects, and sensitivity, specificity, accuracy, NPV, PPV, likelihood ratios, and AUC were then using the same 0.5 cut-off. A graphic representation of classification of each group can be seen in Figure 4-5, with the grey dashed line representing the 0.5 cut-off. The age corrected training model also gave a slightly improved sensitivity and specificity compared to the uncorrected model (sens=91.00%; spec=85.20%), and can be seen in Table 4-6 (2,3,12,13).

Figure 4-4 – *Structural MRI measures of importance for the separation between AD and healthy controls in the age corrected model. Measures with high variance (each end) are more likely to have an impact on group separation. Structures with a negative covariance have a lower value in AD subjects, while structures with positive covariance have higher values in control subjects. Measures are listed with jack-knifed confidence intervals, and those that include zero have low reliability for distinguishing groups.*

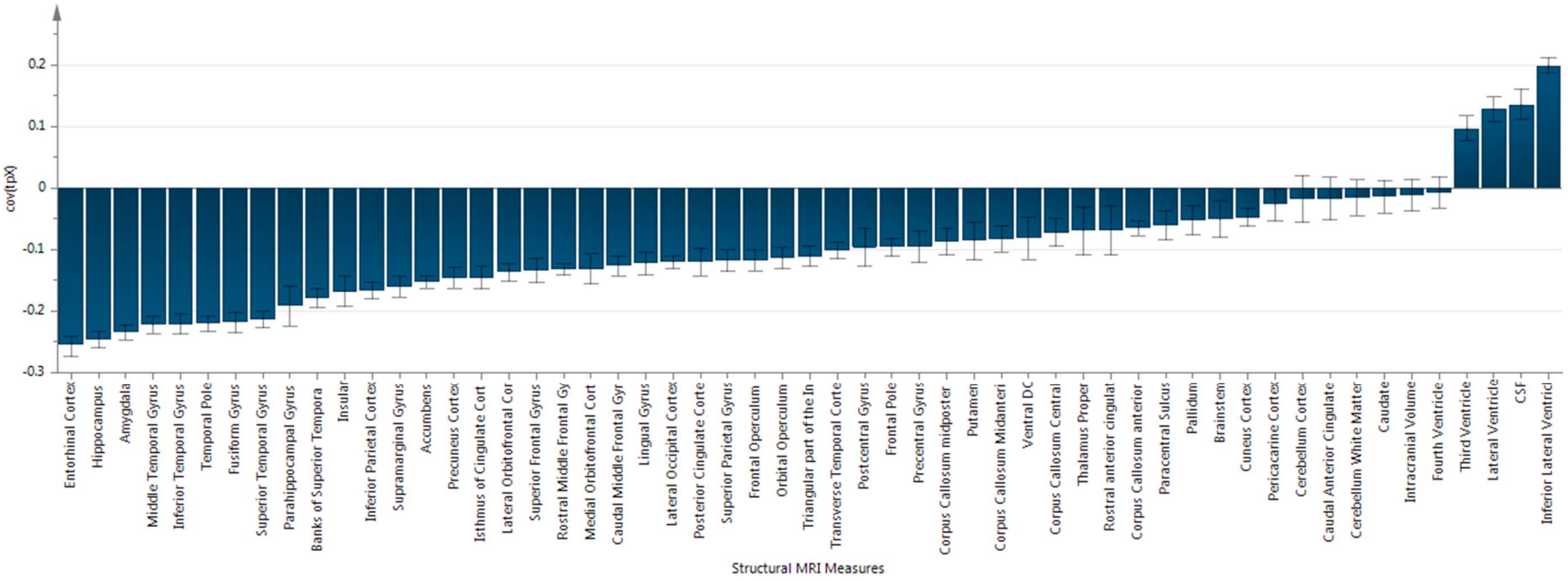


Figure 4-5 *– Class separation of the age corrected training model using 7-fold CV; grey dashed line represents 0.5 cut-off. Orange triangles represent AD subjects and Blue triangles represent healthy control subjects.*

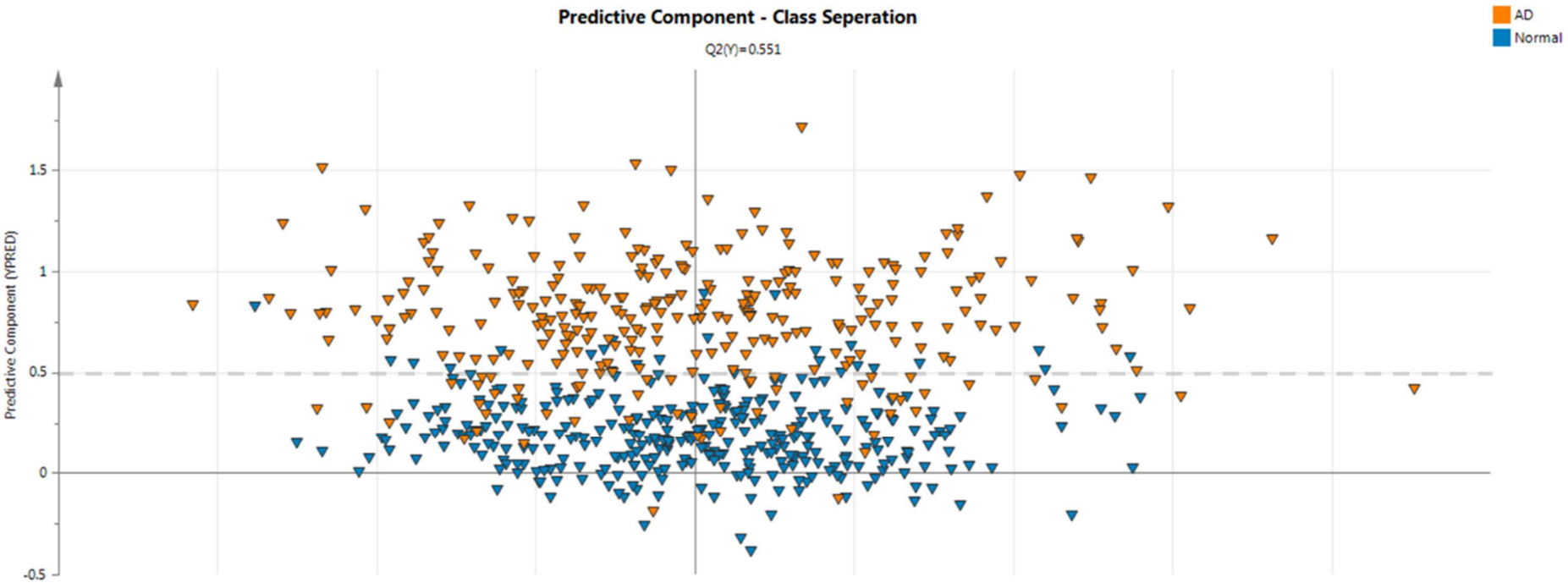


Table 4-6 – Age Corrected Model Description

Sensitivity	Specificity	Accuracy	LR+	LR -	PPV	NPV	AUC	Q^2	R^2
91.00%	85.20%	87.60%	6.15	0.11	90.98%	81.52%	0.945	0.551	0.576

4.3.3 Application of OPLS in a Memory Clinic Cohort

4.3.3.1 OPLS application with 0.5 cut-off

Because this model is based on AD and healthy controls, the model can only predict whether a given participant (or brain) is classified as more AD-like or more control-like.

Using the same 0.5 cut-off, we used the AD Atrophy score to determine whether a subject had a more control-like (AD Atrophy score < 0.5) or more AD like (AD Atrophy score > 0.5) brain. We did this with two AD Atrophy scores for each person, one using the age correction method described earlier, and one without (Falahati et al., 2016). For age corrected AD Atrophy score, the average age for participants classified as control-like was 71.89 (±11.50) and 74.79 (±9.41) for AD-like. For age uncorrected AD Atrophy score, the average control-like participant was 68.92 (±11.31) and 77.50 (±7.83) for AD-like participant (Table 4-7). It is clear the age correction removes the atrophy due to normal ageing, and therefore brings the average ages of AD-like and control-like participants closer together.

Table 4-7 – Differences in average age between groups using age corrected versus uncorrected ages.

	Uncorrected	Corrected
AD-Like	77.50 (±7.83)	74.49 (±9.41)
Control-Like	68.92 (±11.31)	71.89 (±11.50)

Participants were broken down into AD-like and control-like categories by diagnosis, as previously described. The AD diagnostic group had a substantial percentage of patients with AD-like classifications for both age corrected (67.0%) and age uncorrected (72.6%) AD Atrophy scores. A complete list

percentages of AD-like versus control-like participants (both age corrected and age uncorrected) for each diagnosis are listed in Table 4-8. Graphs of the distribution of AD-like and Control-like participants for each diagnosis is depicted in Figure 4-6 for age uncorrected figures, and Figure 4-7 for age corrected figures.

Table 4-8 – *Classifications of AD-Like and Control-Like based on Diagnosis using a 0.5 cut-off*

	Uncorrected		Corrected	
	AD-Like	**CTL-Like**	**AD-Like**	**CTL-Like**
Alzheimer's Disease	72.6%	27.4%	67.0%	33.0%
Mild Cognitive Impairment	33.3%	66.7%	34.4%	65.6%
Mixed Dementia	73.0%	27.0%	61.9%	38.1%
Vascular Dementia	42.9%	57.1%	46.4%	53.6%
Other Dementia	30.0%	70.0%	30.0%	70.0%
Unspecified Dementia	60.6%	39.4%	63.6%	36.4%
Other Psychiatric Condition	41.7%	58.3%	51.4%	48.6%
No Diagnosis	68.0%	32.0%	72.0%	28.0%

Figure 4-6 *– Bar Chart of AD-like versus Control-like subjects using age uncorrected figures and a 0.5 cut-off.*

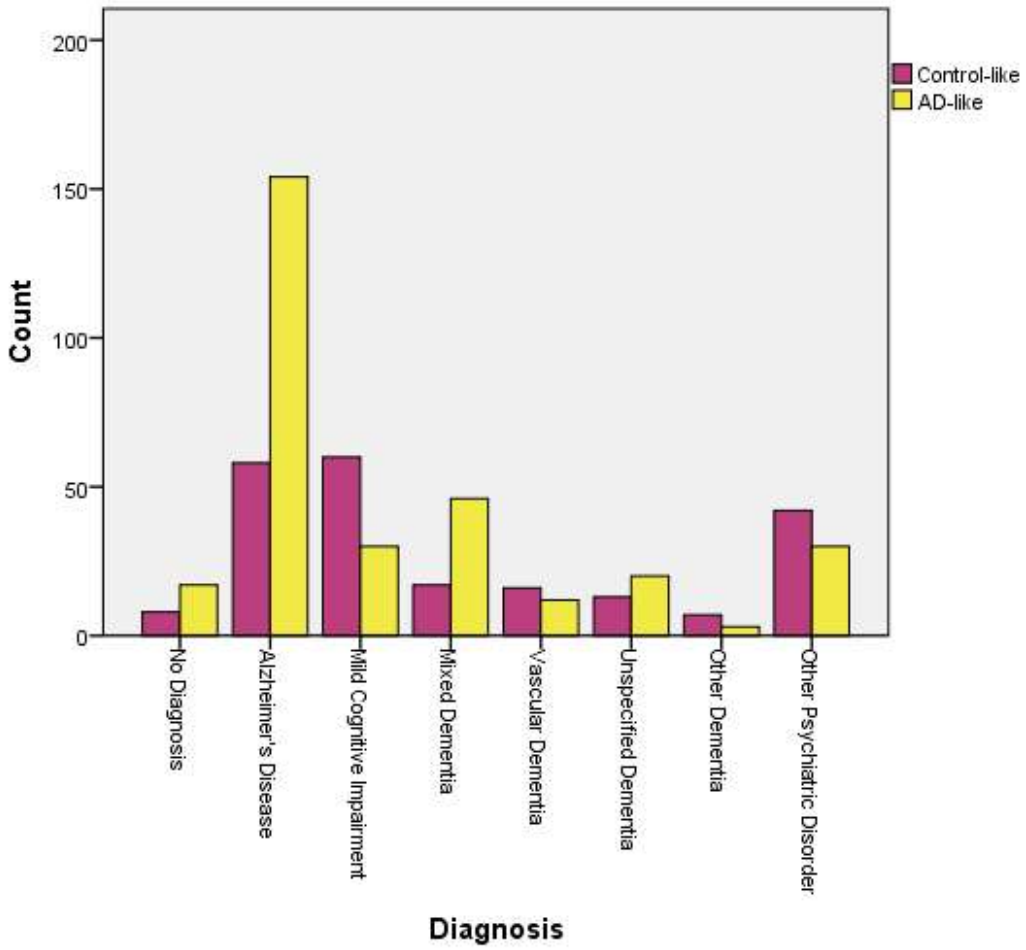
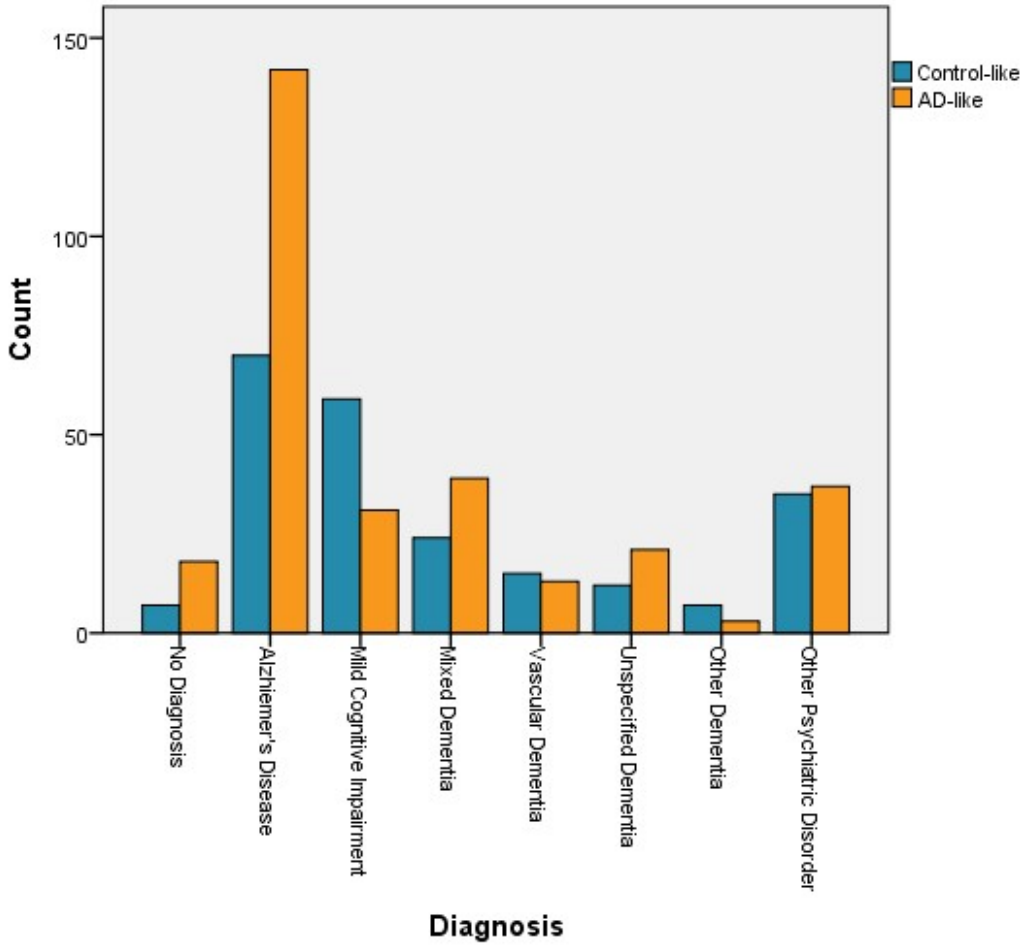


Figure 4-7 – *Bar Chart of AD-like versus Control-like subjects using age corrected figures and a 0.5 cut-off.*



4.3.3.2 OPLS application with 0.39 cut-off

Recent studies have shown that it may be more appropriate to use a 0.39 cut-off instead of a 0.5 cut-off, as there is more variation within AD patients than within healthy controls. Much of the variation in healthy controls is due to age related atrophy, which should be minimised using the age correction method described earlier (Falahati et al., 2017). This cut-off is created based on one standard deviation

greater than the average AD Atrophy score for a healthy control, as described in *section 4.2.3.2.1*. This cut-off did improve classification, with the AD diagnostic category having 76.9% (age corrected) and 82.1% (age uncorrected) of participants being classified as having an AD-like brain. A complete list percentages of AD-like versus control-like participants (both age corrected and age uncorrected) for each diagnosis, with this lower cut-off, are listed in Table 4-9. Graphs of the distribution of AD-like and Control-like participants for each diagnosis is depicted in Figure 4-8 for age uncorrected figures, and Figure 4-9 for age corrected figures. In order to better visualise the changes due to this new 0.39 cut-off, Table 4-10 includes the % increase in AD-like classification for each disease category.

Table 4-9 – *Classifications of AD-Like and Control-Like based on Diagnosis using a 0.39 cut-off.*

	Uncorrected		Corrected	
	AD-Like	**CTL-Like**	**AD-Like**	**CTL-Like**
Alzheimer's Disease	82.1%	17.9%	76.9%	23.1%
Mild Cognitive Impairment	52.2%	47.8%	43.3%	56.7%
Mixed Dementia	82.5%	17.5%	79.4%	20.6%
Vascular Dementia	67.9%	32.1%	57.1%	42.9%
Other Dementia	50.0%	50.0%	40.0%	60.0%
Unspecified Dementia	69.7%	30.3%	72.7%	27.3%
Other Psychiatric Condition	47.2%	52.8%	66.7%	33.3%
No Diagnosis	80.0%	20.0%	80.0%	20.0%

Figure 4-8 – *Bar Chart of AD-like versus Control-like subjects using age uncorrected figures and a 0.39 cut-off.*

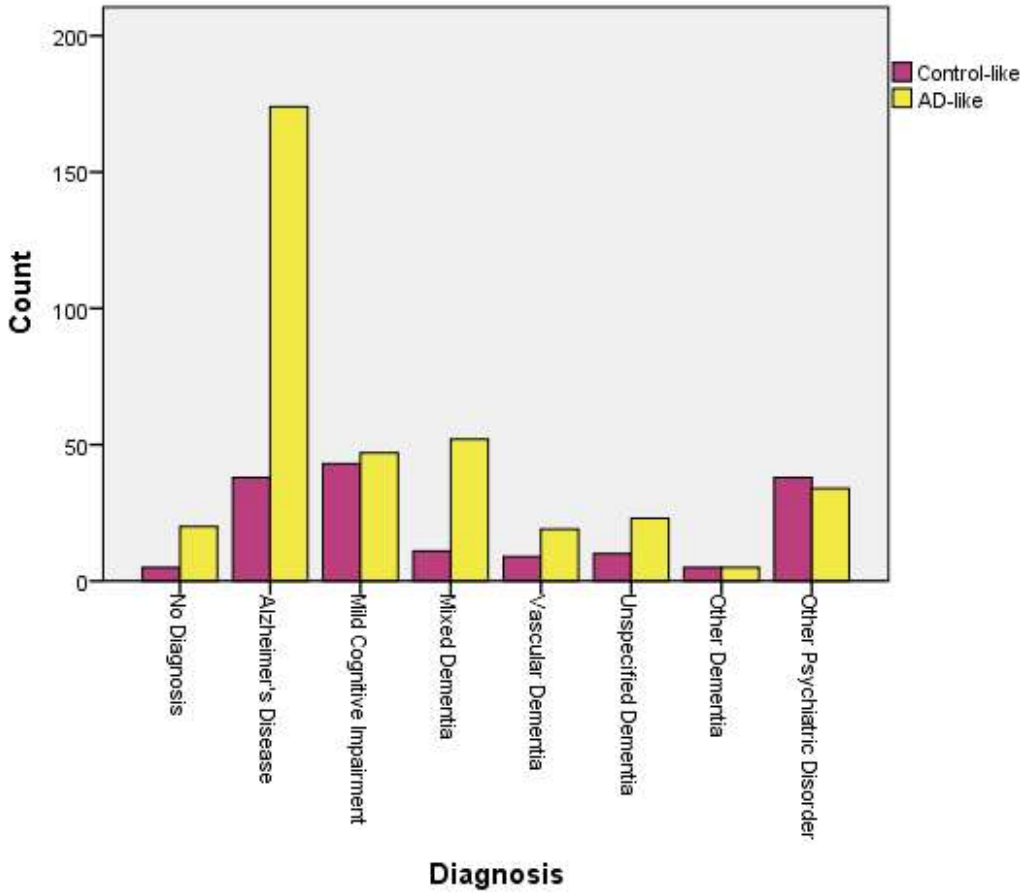


Figure 4-9 – Bar Chart of AD-like versus Control-like subjects using age corrected figures and a 0.39 cut-off.

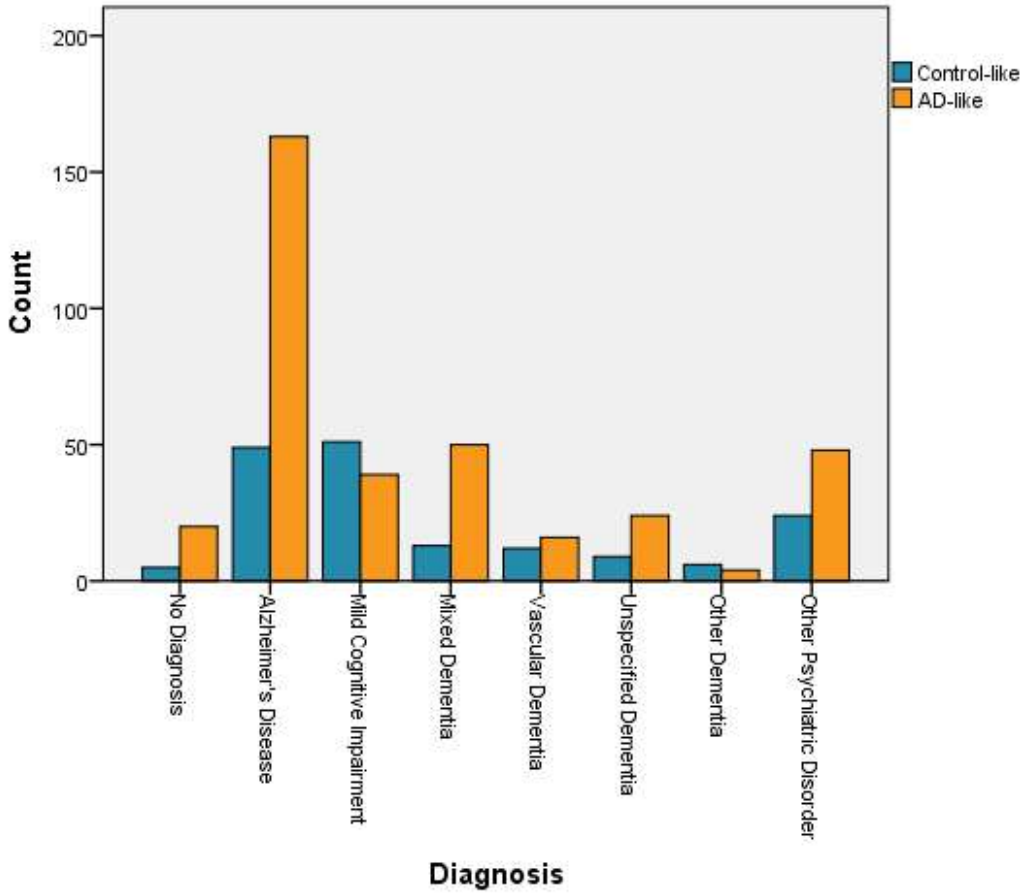


Table 4-10 – Change in classification percentage using a 0.39 versus a 0.5 cut-off.

	Uncorrected			corrected		
	0.5	**0.39**	**% CHANGE**	**0.5**	**0.39**	**% CHANGE**
	AD-Like	**AD-Like**		**AD-Like**	**AD-Like**	
Alzheimer's Disease	72.6%	82.1%	*9.5*	67.0%	76.9%	*9.9*
Mild Cognitive Impairment	33.3%	52.2%	*18.9*	34.4%	43.3%	*8.9*
Mixed Dementia	73.0%	82.5%	*9.5*	61.9%	79.4%	*17.5*
Vascular Dementia	42.9%	67.9%	*25.0*	46.4%	57.1%	*10.7*
Other Dementia	30.0%	50.0%	*20.0*	30.0%	40.0%	*10.0*
Unspecified Dementia	60.6%	69.7%	*9.1*	63.6%	72.7%	*9.1*
Other Psychiatric Condition	41.7%	47.2%	*5.5*	51.4%	66.7%	*15.3*
No Diagnosis	68.0%	80.0%	*12.0*	72.0%	80.0%	*8.0*

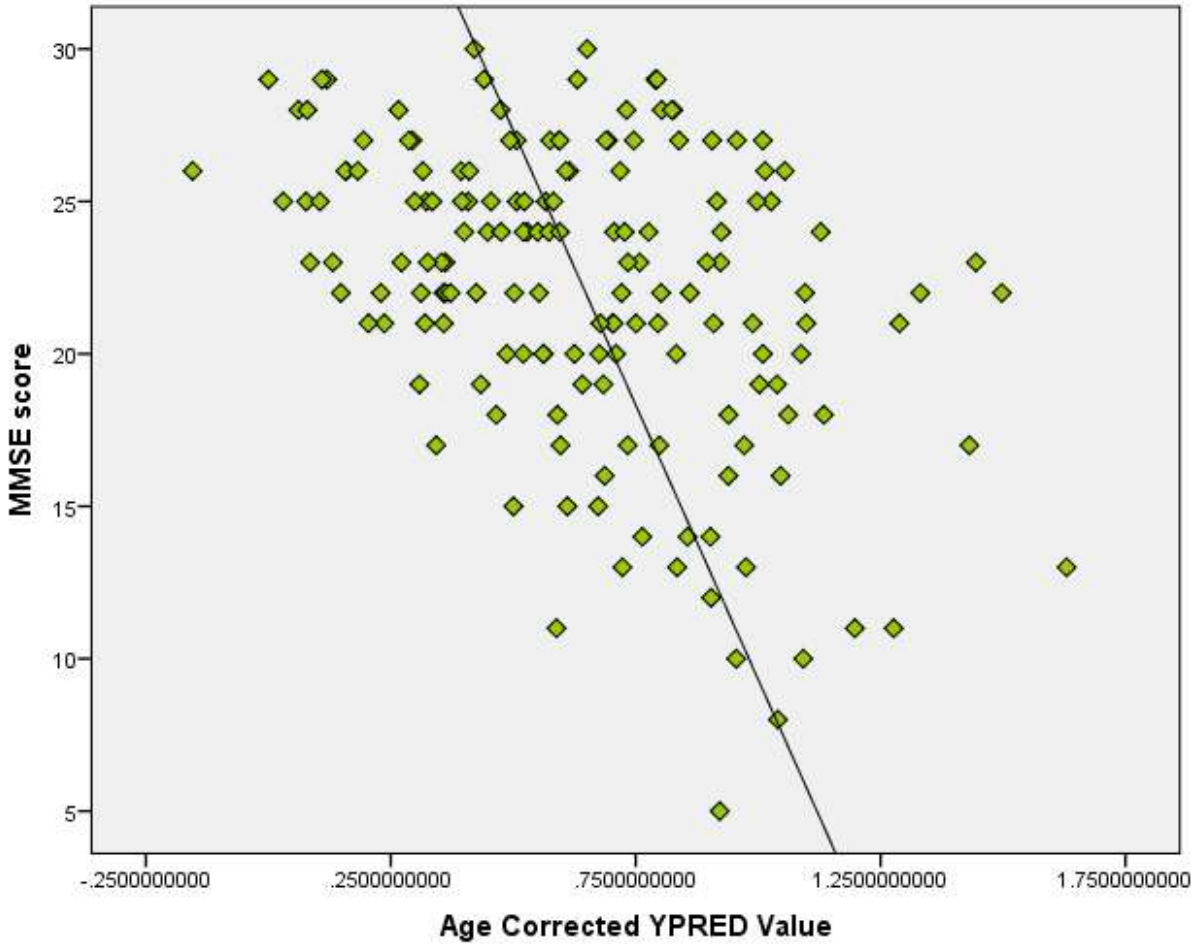
4.3.3.3 MMSE vs Y Predicted value – correlation

To follow up on the previous chapter's (*Chapter 3: Correlation of MMSE Score and Hippocampal Volume in a Memory Clinic Cohort*) findings, correlations were calculated between a participants AD Atrophy score (both age corrected and age uncorrected) and MMSE score. The correlations and p-values for each disease category can be found in Table 4-11, and a scatter-plot depicting the correlation between age corrected AD Atrophy scores and MMSE score for the AD patient group can be found in Figure 4-11

Table 4-11 – *Correlation of MMSE and AD Atrophy score within diagnostic categories. * denotes significance at p<.001 level*

	Uncorrected		Corrected	
	R^2	**p-value**	**R^2**	**p-value**
Alzheimer's Disease	-0.349	<0.001*	-0.411	<0.001*
Mild Cognitive Impairment	-0.251	0.580	-0.198	0.136
Mixed Dementia	-0.182	0.243	-0.287	0.062
Vascular Dementia	-0.089	0.693	0.070	0.756
Other Dementia	-0.573	0.083	-0.457	0.185
Unspecified Dementia	0.111	0.613	0.052	0.815

Figure 4-10 – Scatter-plot MMSE score and age corrected AD Atrophy score; only including AD subjects.



4.4 DISCUSSION

4.4.1 Model Performance

The model's sensitivity of 90.0% indicates it performed well at distinguishing AD and healthy control brains. Several other studies have used similar models based on the ADNI and AddNeuroMed datasets, and found the same or similar results (Spulber et al., 2013; Westman, Cavallin, Muehlboeck, et al., 2011b; Westman, Simmons, Muehlboeck, et al., 2011; Westman, Wahlund, Foy, et al., 2011; Westman

et al., 2013). The classification of memory clinic patients did not perform as well as the training set, but this is to be expected due to the heterogeneity of a memory clinic cohort. This may be due to the strict inclusion criteria in research cohorts that is not present in the clinic, such as lack of comorbidities or specific neuropsychiatric test scores.

An interesting point is that 80% (at 0.39 cut-off) of patients that ultimately received no diagnosis (such as 'Persons encountering health services for examination and investigation') were classified as more AD-like. At first glance, this can be interpreted as a misclassification, however it is important to remember there are no healthy controls in this sample. It makes sense that many may be classified as more AD-like when they are suffering from subjective memory complaints, and ultimately visiting a memory service. It may be that they go on to develop MCI or AD in the future.

OPLS models based on healthy controls and AD patients are able to predict conversion to AD from MCI reasonably well in research cohorts with longitudinal data (Spulber et al., 2013). Conversely, it is expected that the classification of MCI patients would be quite mixed (corrected 0.39 cut-off for MCI: 56.7% Control-like; 43.3% AD-like) because most patients with MCI would not have the pronounced atrophy of someone with AD yet. This mixed classification result may be a representation of MCI patients who will convert versus those who will not, and it would be very interesting to follow these patients and examine their diagnoses at one year follow up. Additionally, this mixed classification could be due to the heterogeneity of pathology that underlies MCI. While 60-70% of cases of amnestic MCI can be attributed to AD pathology mixed with another type of dementia pathophysiology such as white matter changes and cerebrovascular disease, or Lewy body disease (Jicha et al., 2006; Ronald C. Petersen et al., 2006). MCI patients in this cohort did not only included amnestic MCI, but may include other types, such as MCI due to vascular changes, that might share the same pattern of AD-like pathology.

MD patients were also highly classified as AD-like (corrected 0.39 cut-off: 79.4%). This was expected as MD patients are considered to have both neuropathologies of AD and VaD present in one patient. Because any vascular changes are not accounted for in classification, they would be classified as AD rather than healthy controls.

Lastly, it is important to remember the gold standard for an AD diagnosis is still histological confirmation of neuropathology defined by Braak and Braak (Braak & Braak, 1991; G. McKhann et al., 1984). While there is movement away from this as the standard, clinical diagnosis is also not flawless. One study found that clinician diagnosis only achieves a sensitivity somewhere between 70.9% and 87.3% (Beach, Monsell, Phillips, & Kukull, 2012). Clinician diagnoses consider very many factors, including anecdotal evidence from caretakers and family, which can be useful for identifying more subtle changes that may not yet have manifested in brain morphometry.

4.4.2 Age-Correction

While other studies have found age-correction to improve models, the AD group classification was lower when using age-corrected values versus uncorrected values (0.5 cut-off= 67.0% vs 72.6%; 0.39 cut-off=76.9% vs 82.1% respectively). This is probably due to the heterogeneity of a clinical cohort as compared to a research cohort. The previous studies used ADNI and AddNeuroMed, which have strict inclusion criteria, such as patients must have an MMSE between 20-26 to be in the AD group. These studies found misclassified participants had significantly higher MMSE scores than those in the AD and MCI group that were correctly classified. Because this is a purely clinical cohort, diagnoses are based purely on clinician discretion, and it was found that many patients diagnosed with AD had an MMSE score above 26. The age-correction in our cohort might be factoring out the existing changes, that may be being classified as neuropathological by clinicians, despite the fact that these few have a higher than average MMSE for an AD patient. There are several issues with MMSE, including ceiling effects and the

lack of ability to pick up very subtle changes in highly cognitively able people, such as those with many years of education (Mitchell, 2009). Clinicians may be aware of these issues with the MMSE, and have better insight on diagnosing patients that may indeed have AD while performing reasonably well on the MMSE.

4.4.3 Cut-off Values

While previous work has been based on a 0.5 cut-off for AD Atrophy score categorisation, there is some recent work that has moved to using a 0.39 cut-off. The argument is while there is intersubject variability in normal values, AD is a heterogenous disorder and there is probably greater variation with the AD group than within the healthy control group. Therefore, using the 0.5 cut-off may not account for the likely much larger variation in AD patients than healthy controls. Previous work has showed how heterogenous AD pathology and atrophy can be in AD, and this may be better reflected in the use of a lower cut-off (D. Ferreira et al., 2015; Lam, Masellis, Freedman, Stuss, & Black, 2013; Noh et al., 2014; Pereira et al., 2014a). Part of the variation in healthy controls is due to normal ageing, which can be reduced by applying the age correction technique used in the current study. This lower cut-off based on one standard deviation above an average value for healthy controls was shown to increase the sensitivity for classifying AD subjects, and it may be beneficial to consider using this instead of the previously used 0.5 cut-off in the future (Falahati et al., 2017).

Generally, more patients are classified as AD-like instead of control-like, and this is true for the other diagnostic categories that listed in this analysis as well. Interestingly, for the uncorrected AD Atrophy scores the largest percent change in sensitivity due to the revised cut-off value was seen in the VaD and Other Dementia categories (25% and 20% respectively). Since only the people who fall into this mid .39 - .5 range would change, hence the largest patient groups that have this range most populated are not in the AD category. Those in the AD group are likely to be clustered on the higher end of the 0-1 range,

with just a few that fall on the lower end and would be influenced by the new cut-off. For age-corrected AD Atrophy scores, the largest percent changes were found in MD and other psychiatric conditions (17.5% and 15.3% respectively), however there was a substantial increase in the VaD category (10.7%).

4.4.4 AD Atrophy score and MMSE Correlation

As expected, AD Atrophy scores and MMSE score were positively correlated in the AD group, but not the other groups. This is expected, as cognitive functioning, as measured by MMSE, in AD is closely related to brain atrophy (G. Frisoni et al., 2002). Unlike the classification, correlation improved with age-correction. As previously discussed, this makes sense because of the large number of AD patients with higher MMSE scores. Since the age-correction removed atrophy due to natural ageing, the remaining AD Atrophy score is more representative of atrophy due to AD, which would be reflected in the MMSE score.

4.4.5 Limitations

4.4.5.1 Healthy Controls

Nearly all previous studies of this nature compare AD and MCI patients to healthy controls, while this study did not have a healthy control group. Some might consider this a limitation; however it is more representative of a clinical setting as clinicians will not have to distinguish between AD and healthy controls, but different forms of dementia.

However, one limitation is the age correction was based on the normal controls from the ADNI / AddNeuroMed sample and may not be representative of a population based sample.

4.4.5.2 Educational Differences

There was a significant difference between years of education between healthy controls and AD subjects in the ADNI/AddNeuroMed training set. While the exact relationship is unclear, years of education can

influence hippocampal atrophy in AD (Shpanskaya et al., 2014). Additionally, low education levels have been found to be a potential risk factor for dementia (Meng & D'Arcy, 2012). According to a recent study, less education (defined as no secondary school) poses a relative risk of 1.59 for developing dementia, and has the second highest population attributable factor (the theoretical percent reduction in new cases over a given time if the risk factor was eliminated completely (Livingston et al., 2017). Because of the obvious importance of education level in dementia development, a significant difference between the groups could potentially introduce a bias in the model. However, previous models including years of education as a variable have not been shown to perform differently (Aguilar et al., 2013).

4.4.6 Future Directions

As mentioned earlier, the mixed classification of MCI patients may be representative of which patients will go on to develop AD in the future. As previously shown, similar algorithms are capable of distinguishing patients who go on to convert to AD from those who either revert back to normal cognition or remain in the MCI diagnostic category (Westman et al., 2012). It would be interesting to follow these patients longitudinally, and compare their current classification to any future diagnoses.

In the future, it would be interesting to train the OPLS algorithm on different types of dementia instead of one type versus healthy controls. Creating a model that uses VaD and AD, instead of AD versus healthy controls, could create scores based on volumetric data and white matter hyperintensity and vascular data. Scores could then predict if someone was more AD or VaD like, or a middle score of 0.5 could suggest a diagnosis of MD.

As other studies have found improvement in classification with the addition of other modalities, it may also improve classification in a clinical cohort (Westman, Wahlund, Foy, et al., 2011; Westman et al., 2012). MMSE and other neuropsychiatric tests, blood biomarkers, and potentially CSF measures may be

present in EHR and could improve the classification results. Additionally, if future research techniques such as segmentation of white matter hyperintensities in vascular dementia become included in EHR, these could also be used in the analysis.

4.5 CONCLUSION

The multivariate analysis technique, OPLS has now been successfully performed in a memory clinic cohort. While the models did not classify AD patients from a memory clinic cohort with as high of an accuracy as they did in research cohorts such as ADNI and AddNeuroMed, they still performed reasonably well. Especially with the addition of other measures such as CSF or cognitive scores, OPLS may be a useful clinical tool in the future.

5 White Matter Hyperintensities and the Underdiagnosis of Mixed Dementia in Memory Clinic Cohorts.

5.1 Introduction

5.1.1 Mixed Dementia

While Alzheimer's Disease (AD) is considered the most common form of dementia, most dementia cases have been found to exhibit mixed pathologies, with both AD and vascular components (Gustavo C. Román, 2002; Schneider, Arvanitakis, Bang, & Bennett, 2007). Despite this large portion of dementia patients that suffer from mixed dementia (MD), compared to AD there is relatively little research on the disorder.

While vascular etiologies cause a large proportion of dementia cases, exact figures can be difficult to calculate due to the varied criteria for vascular cognitive impairment (VCI) (De Reuck et al., 2016; Rockwood et al., 2000). There is debate over what pathologies to include in the diagnosis of vascular dementia (VaD) or MD, and this can include any kind of vascular brain injury such as: large macroscopic, lacunar, or microscopic infarcts, haemorrhages, and vessel pathologies such as cerebral amyloid angiopathy, and intracranial atherosclerosis.

Many of these vascular problems occur in the general population. It is estimated that somewhere between 16-46% of elderly people have microinfarcts, and this increases to 51% in the oldest old (Arvanitakis, Leurgans, Barnes, Bennett, & Schneider, 2011; Corrada, Sonnen, Kim, & Kawas, 2016; Ince et al., 2017; Kapasi, DeCarli, & Schneider, 2017; Lenore J. Launer, Hughes, & White, 2011; Schneider, Arvanitakis, et al., 2007). Two community based cohorts, the Religious Order Study and the Memory and Aging Project, have shown nearly 75% of people with a pathological dementia diagnosis have one or

more vascular pathologies in addition to their cognitive impairment (Bennett et al., 2013; Bennett, Schneider, Buchman, et al., 2012; Bennett, Schneider, Arvanitakis, & Wilson, 2012; Kapasi et al., 2017).

Autopsy studies show many patients have both vascular and degenerative causes of dementia, and MD may be a more common form of dementia than currently recognised (K. A. Jellinger & Attems, 2007; Korczyn, 2002). The literature states MD prevalence varies widely in autopsy studies, from 0-55% (Zekry, Hauw, & Gold, 2002).

5.1.2 Vascular Pathologies and Cognitive Impairment

There are many questions raised by the literature on MD, such as which kinds of vascular brain injury induce cognitive impairment and lower the threshold for AD development, and do specific vascular pathologies potentiate AD development and drive the neurodegenerative processes, does AD potentiate the vascular changes, or both (Kapasi et al., 2017).

There are several studies that indicate the presence of multiple macroscopic infarcts has more impact on cognitive impairment than the size of a single infarct (Schneider, Boyle, Arvanitakis, Bienias, & Bennett, 2007; Troncoso et al., 2008; White, 2009). The overall size, number, and position of microinfarcts can also have significant impact on cognitive ability, and are important when determining a dementia diagnosis (Arvanitakis et al., 2011; Troncoso et al., 2008). Various autopsy and positron emission tomography (PET) studies indicate that AD pathology and VBI contribute additively to the risk of dementia, but through independent processes (Chui & Ramirez-Gomez, 2015). Many individuals suffer both types of pathologies, as seen in MD, and this may have an additive effect on cognitive impairment (Snowdon et al., 1997).

5.1.3 Current Diagnostic Standards

The current diagnostic categories for VaD are based on a severity threshold, which are used for disease diagnosis at the later stages, when treatments are not as effective. There has been discussion of moving

towards the use of Vascular Cognitive Impairment (VCI), to identify impairments at an earlier phase (Hachinski & Bowler, 1993; O'Brien et al., 2003; Sachdev et al., 2014). While it is clear vascular etiologies cause a significant portion of dementia, the exact figures remain unclear because there is varied criteria for what constitutes VCI (De Reuck et al., 2016; Rockwood et al., 2000). Unlike AD, the cognitive impairment profiles for VCI and VaD are highly variable, and dependent on the size and location of the vascular brain injury (VBI) (Sachdev et al., 2014). VaD is not one disease, there are various etiologies, not all of which are well characterised, and white matter changes in magnetic resonance imaging (MRI) do not always correspond with symptoms (Hunt et al., 1989; Kurt A. Jellinger, 2008). The official diagnostic criteria for VaD as stipulated by the Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke (NINDS) and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) only requires a patient to experience severe cognitive decline that impedes daily functioning and indication of cerebrovascular disease (CVD) by clinical examination or brain imaging (G. C. Román et al., 1993).

VaD diagnoses are normally based on cardiovascular risk factors and interviews, and often may not assess underlying pathology (Barkhof, 2011). Non-significant white matter changes may also be mistaken for VaD, and lead to overdiagnosis (Niemantsverdriet et al., 2015). This may lead to MD being misdiagnosed as VaD, because there is little to no assessment of underlying AD pathology. Additionally, misdiagnosis may work in the opposite direction, as once an AD diagnosis is obtained, there may be less concentration on the investigation of cardiovascular risk factors or white matter changes. One study looking at varying degrees of CVD showed that CVD was often clinically underestimated in people with an AD diagnosis (Reed et al., 2004). The reform of these diagnostic standards potentially have great use, as there is evidence that reduction of vascular risk factors may lead to a decline in the incidence of dementia (Satizabal, Beiser, & Seshadri, 2016).

5.1.3.1 Use of Visual Rating Scales for White Matter Changes

In clinical practice, visual rating scales are often used to determine the severity of white matter changes in memory clinic patients. The Fazekas scale (Fazekas et al., 1987) and the Scheltens WMC (white matter changes) scale (P. Scheltens et al., 1993) are the most popular (Xiong & Mok, 2011). The Fazekas scale is simple and easy for clinicians to use quickly. More complex scales exist such as the Age Related White Matter Changes (ARWMC) scale, which can be used to assess WMH in various regions, but these can be time consuming and therefore are not always practical for clinical use (L. O. Wahlund et al., 2001). A wide array of visual rating scales exist, with varying regional areas of interest (such as deep WHM or periventricular WMH), but because the criteria vary they can provide diverse scores for the same patient (Mäntylä et al., 1997). Discrepancies between these various scales may cause inconsistencies. Visual rating scales are also subject to ceiling effects, and do not provide quantitative evidence as automated methods do.

5.1.4 White Matter Hyperintensities

White matter hyperintensities (WMH) are the most used indication of vascular changes and VBI on MRI (Wardlaw et al., 2013). They can be indicative of cerebral small vessel disease, and may originate from a variety of pathologies including ischemic tissue damage caused by arteriosclerosis, vasogenic edema induced by periventricular venous collagenosis, or cerebral amyloid angiopathy (Black, Gao, & Bilbao, 2009; Alida A. Gouw et al., 2011; Haglund & Englund, 2002; Moody, Brown, Challa, & Anderson, 1995; O'Sullivan et al., 2008; Pantoni, 2010; E. E. Smith & Eichler, 2006; Viswanathan & Chabriat, 2006; Wardlaw et al., 2013). WMH as a biomarker are associated with increased age, cardiovascular risk factors, and future development of Mild Cognitive Impairment (MCI) and AD (C. DeCarli et al., 2001; Ramirez, McNeely, Scott, Stuss, & Black, 2014; Yoshita et al., 2006). Due to their use in the current dementia literature, WHM lesion load was used in this study to examine the effects of VBI on dementia diagnosis in a memory clinic cohort.

5.1.5 Rationale and Hypotheses

MD is categorised by neuropathologies typical of AD, such as hippocampal atrophy or a high AD severity score derived from the previous orthogonal projection to latent structure (OPLS) multivariate image analysis using regional FREESURFER measurements, and VaD, such as WMH. Following this logic, patients in our current memory clinic cohort were broken down into four categories based on theoretical neuropathologies: normal-like (no abnormal hippocampal atrophy/low AD severity score or WMH), AD-like (pronounced hippocampal atrophy/high AD severity score with no WMH), VaD-like (little hippocampal atrophy/a normal AD severity score but a large amount of WMH), and MD-like (both pronounced hippocampal atrophy/high AD severity score and presence of significant WMH).

In this study, two different sets of cut-offs were used, one using the Memory Clinic's median value, and one using a one-third cut-off, both described below in *section 5.2.3*. For each of these cut-offs, two different sets of groups were formed. One used average normalised hippocampal volume as a measure of AD pathology, while the other uses the AD severity score as measured by OPLS (as described in *Chapter 4: OPLS in a Memory Clinic Cohort*). This resulted in four separate exploratory analyses: 1. Group separation determined by WMH load and hippocampal volume using a median score as a cut-off, 2. Group separation determined by WMH load and AD severity score using a median score as a cut-off, 3. Group separation determined by WMH load and hippocampal volume using a 33rd percentile score as a cut-off, and finally 4. Group separation determined by WMH load and AD severity score using a 33rd percentile score as a cut-off. All groups were then compared to ultimate diagnosis received in the memory clinic. The goal of this study was to investigate the distribution of mixed dementia diagnoses depending on severity of AD-like atrophy and VaD pathologies, and investigate the potential under-diagnosis of MD in memory clinics.

5.2 METHODS

5.2.1 Demographics

The memory clinic cohort was comprised of patients from the South London and Maudsley NHS trust (SLaM), who had been referred to a memory clinic after experiencing memory difficulties. The demographic information for the memory clinic cohort and inclusion criteria can be found in *Chapter 2: The Biomedical Research Centre Memory Clinic Cohort*. For this study, we used a total of 589 participants whose scans passed quality control checks as described in *Chapter 2* (*section 2.2.2*), and diagnostic information. Additionally, as in previous chapters, the memory clinic cohort was broken down into diagnostic categories. Out of the 589 subjects that were included in this study, 334 had a diagnosis in their electronic health record. These 334 subjects had a diagnosis that fit into one of the following categories: AD, MCI, MD, VaD, unspecified dementia, other dementia (such as Parkinson's Dementia or Pick's disease) and other psychiatric condition (such as anxiety or depression).

5.2.2 Imaging

5.2.2.1 MRI acquisition

The image acquisition and quality control procedures for the BRCMEM cohort was based on ADNI and AddNeuroMed parameters, and is described in detail in *Chapter 2: The Biomedical Research Centre Memory Clinic Cohort, section 2.2.2*.

5.2.2.2 FREESURFER Volumetric Analysis

The T1 images were analysed with the FREESURFER pipeline version 5.3.0 (http://surfer.nmr.mgh.harvard.edu/) to produce regional cortical thickness and subcortical volume measures. The pipeline includes removal of non-brain tissue using a hybrid watershed/surface deformation procedure (F. Ségonne et al., 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep grey matter volumetric structures (Bruce Fischl et al., 2002; Bruce Fischl, van der Kouwe, et al., 2004; F. Ségonne et al., 2004) intensity normalisation (Sled et al., 1998), tessellation of the grey matter white matter boundary, automated topology correction (B. Fischl et al., 2001; Florent Ségonne et al., 2007), and surface deformation following intensity gradients to optimally place the grey/white and grey/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (A. M. Dale et al., 1999; Anders M. Dale & Sereno, 1993; B. Fischl & Dale, 2000). Once the cortical models are complete, registration to a spherical atlas takes place which utilises individual cortical folding patterns to match cortical geometry across subjects (B. Fischl et al., 1999). This is followed by parcellation of the cerebral cortex into units based on gyral and sulcal structure (Desikan et al., 2006; Bruce Fischl, van der Kouwe, et al., 2004). The pipeline generated 68 cortical thickness (34 from each hemisphere) and 21 regional subcortical volumes (Table 5-1). This segmentation approach has been used for multivariate classification of Alzheimer's disease and healthy controls (Westman, Wahlund, Foy, et al., 2011), neuropsychological-image analysis (Yawu Liu et al., 2011; Yawu Liu, Paajanen, Zhang, et al., 2010), imaging-genetic analysis (Yawu Liu, Paajanen, Zhang, et al., 2010) and biomarker discovery (Thambisetty et al., 2010).

Table 5-1 *– List of FREESURFER outputs, including all Cortical Thicknesses and Subcortical structures used in the OPLS analysis*

Cortical Thicknesses (both Right and Left)	Subcortical structures
Banks of superior temporal sulcus	Third ventricle
Caudal anterior cingulate	Fourth ventricle
Caudal middle frontal gyrus	Brainstem
Cuneus cortex	Corpus callosum anterior
Entorhinal cortex	Corpus callosum central
Fusiform gyrus	Corpus callosum midanterior
Inferior parietal cortex	Corpus callosum midposterior
Inferior temporal gyrus	Corpus callosum posterior
Isthmus of cingulate cortex	CSF
Lateral occipital cortex	Accumbens
Lateral orbitofrontal cortex	Amygdala
Lingual gyrus	Caudate
Medial orbitofrontal cortex	Cerebellum cortex
Middle temporal gyrus	Cerebellum white matter
Parahippocampal gyrus	Hippocampus
Paracentral sulcus	Inferior lateral ventricle
Frontal operculum	Putamen
Orbital operculum	Lateral ventricle
Triangular part of inferior frontal gyrus	Pallidum
Pericalcarine cortex	Thalamus proper
Postcentral gyrus	Ventral DC
Posterior cingulate cortex	
Precentral gyrus	
Precuneus cortex	
Rostral anterior cingulate cortex	
Rostral middle frontal gyrus	
Superior frontal gyrus	
Superior parietal gyrus	
Superior temporal gyrus	
Supramarginal gyrus	
Frontal pole	
Temporal pole	
Transverse temporal cortex	
Insular	

5.2.2.2.1 Hippocampal Volume Normalisation

Hippocampal volumes used in the analysis were normalised by total intracranial volume (ICV) as determined by FREESURFER segmentation, to control for differences in head size. This was done by creating a ratio of hippocampal volume divided by total ICV. This has been found to be essential in

structural MRI studies, as differences in head size can create gender differences and influence the results (Scahill et al., 2003; J. L. Whitwell et al., 2001). Right and left hippocampal volume was averaged, and then divided by ICV to create one volume for each participant.

5.2.2.3 OPLS analysis

Following the previous chapter (*Chapter 4: OPLS in a Memory Clinic Cohort*) uncorrected y predictive values (ypred) from the Orthogonal Projection to Latent Structures (OPLS) analysis were also used in this study. These ypred values represents a more comprehensive AD atrophy score, indicating whether a patient's brain is more AD-like (a score closer to 1) or more control-like (a score closer to 0). This approach is more thorough than using hippocampal volumes alone, as all cortical thickness and subcortical volumes (Table 5-1) from the FREESURFER output are used to create the score. For complete OPLS methodology, see the Imaging and OPLS analysis sections of the previous chapter (*Section 4.2.2* and *4.2.3* respectively).

5.2.2.4 WMH Analysis

Lesions were segmented by the lesion prediction algorithm as implemented in the LST toolbox version 2.0.15 (www.statistical-modelling.de/lst.html) for SPM 12. This algorithm consists of a binary classifier in the form of a logistic regression model trained on the data of 53 MS patients with severe lesion patterns. Data were obtained at the Department of Neurology, Technische Universität München, Munich, Germany. As covariates for this model a similar lesion belief map as for the lesion growth algorithm (Schmidt et al., 2012) was used as well as a spatial covariate that takes into account voxel specific changes in lesion probability. Parameters of this model fit are used to segment lesions in new images by providing an estimate for the lesion probability for each voxel (Schmidt & Wink, 2017). For the analysis, FLAIR images were used from each subject, and a T1 MPRAGE was used as a reference image. The LST toolbox was chosen as it is a validated, freely available WMH segmentation analysis tool,

which has been used to analyse WMH in prodromal AD patients previously (Svärd et al., 2017). Because the software was originally intended for, and trained on MS patients, all WHM segmentations were visually inspected for quality.

5.2.3 Memory Clinic Group Divisions

The memory clinic cohort was broken down into groups based on markers of AD pathology and VaD pathology using either hippocampal volume or AD atrophy score, and WMH lesion load. When creating cut-off values for group analyses, the entire memory clinic (n=589), including those without a final diagnosis listed, was used.

Using the cut-offs described in the subsequent subsections (*5.2.3.1* and *5.2.3.2*) participants were given a score of 'low' or 'high'. This use of cut-off values based on percentiles in the cohort of interest has been used previously when analysing WHM in dementia (Eckerström et al., 2011; Tuladhar et al., 2015).

5.2.3.1 Cut-off 1 for discriminating 'low' and 'high' groups: Median Values

The first set of groups was created using the median for each measure within the entire memory clinic group (n=589) (Table 5-2). If the participant had a normalised hippocampal volume, AD atrophy score, or WMH lesion load greater than the median they were classified as 'high' and if the value was lower than the median they were classified as 'low'. Using these measures, four groups were created: Normal-like, AD-like, MD-like, and VaD-like (Table 5-3 and Table 5-4).

Table 5-2 – *Median value for each variable of interest, further used as cut-off values for group separation. WMH load measured in mL.*

	Median Value
Normalised Hippocampal Volume	0.00207
White Matter Hyperintensity Load	6.99
AD Atrophy Score	0.507

Table 5-3 – *Group Division based on Hippocampal Volume and White Matter Hyperintensity Lesion Load. High is classified as greater than the Memory Clinic Cohort's median value (0.00207 for hippocampal volume and 6.99 mL for WMH load), whereas Low is classified as less than the median value.*

	Hippocampal Volume	**White Matter Hyperintensity Load**
Normal-like	High	Low
AD-like	Low	Low
MD- like	Low	High
VaD-like	High	High

Table 5-4 - *Group Division based on AD atrophy score and White Matter Hyperintensity Lesion Load (0.507 for AD Atrophy score and 6.99 mL for WMH load). High is classified as greater the Memory Clinic Cohort's median value, whereas Low is classified as less than the median value.*

	AD Atrophy score	**White Matter Hyperintensity Load**
Normal-like	Low	Low
AD-like	High	Low
MD- like	High	High
VaD-like	Low	High

5.2.3.2 Cut-off 2 for discriminating 'low' and 'high' groups: 33rd Percentiles

The second set of groups was created based on values that represented 33% percentiles for each variable (Table 5-5). The problem with using median values is that such a cut-off is not completely representative of disease pathologies in these conditions. For instance, while hippocampal volume is significantly smaller for individuals with AD compared to healthy controls, it is also significantly smaller in patients with VaD when compared to healthy controls, albeit higher than those with AD (Kim et al., 2015). Conversely, AD patients are on average found to have a larger amount of WHM compared to healthy controls (Barber et al., 1999; Benedictus et al., 2014; Maillard et al., 2012). Using a 33rd

percentile cut-off takes these findings into account, and prioritises discrimination between VaD and AD, rather than a form of dementia versus healthy controls.

Table 5-5 – *33% and 66% percentile value for each variable of interest, further used as cut-off values for group separation. Strike-through values indicated these numbers were not used in the cut-offs. WMH load measured in mL.*

	33%	**66%**
Normalised Hippocampal Volume	0.00186	~~0.00226~~
White Matter Hyperintensity Load	~~3.22~~	11.62
AD Atrophy score	~~0.340~~	0.659

AD Atrophy scores or WMH lesion loads higher than the 66th percentile value, or a normalised hippocampal volume measure greater than the 33rd percentile value were classified as 'high'. Conversely, if they were below these values they were considered 'low'. Using these measures, four groups were created again: Normal-like, AD-like, MD-like, and VaD-like (Table 5-6 and Table 5-7).

Table 5-6 – *Group Division based on Hippocampal Volume and White Matter Hyperintensity Lesion Load. High and Low is classified using the cut-offs above (0.00186 for hippocampal volume and 11.62 mL for WMH load).*

	Hippocampal Volume	**White Matter Hyperintensity Load**
Normal-like	High	Low
AD-like	Low	Low
MD- like	Low	High
VaD-like	High	High

Table 5-7 – *Group Division based on AD Atrophy score and White Matter Hyperintensity Lesion Load. High and Low is classified using the cut-offs above (0.659 for AD atrophy score and 11.62 mL for WMH load).*

	AD Atrophy score	**White Matter Hyperintensity Load**
Normal-like	Low	Low
AD-like	High	Low
MD- like	High	High
VaD-like	Low	High

5.2.4 Statistical Analysis

5.2.4.1 Demographics and Imaging Analyses

Average age, MMSE score, WMH load, normalised hippocampal volume and AD Atrophy score were calculated for each diagnostic category. To test for differences between diagnostic groups a one-way analysis of variance (ANOVA) was run with Bonferroni post-hoc tests.

Furthermore, average age, MMSE score, WMH load, hippocampal volume and AD Atrophy score were calculated for each group created.

5.2.4.2 Cut-off 1 for discriminating 'low' and 'high' groups: Median Values

Average age, MMSE score, WMH load, normalised hippocampal volume and AD Atrophy score were also calculated for each group created with the median value cut-offs (Normal-like, AD-like, MD-like, and VaD-like). Two sets of groups were created, one using hippocampal volume and WMH load, and the other using AD Atrophy score and WMH load.

Each group was then broken down by ultimate diagnosis in the memory clinic. Only participants that had a diagnosis listed in their electronic health record (including 'no diagnosis', such as 'Persons encountering health services for examination and investigation') were included in this portion of the analysis (N=334).

5.2.4.3 Cut-off 2 for discriminating 'low' and 'high' groups: 33rd Percentiles

Average age, MMSE score, WMH load, normalised hippocampal volume and AD Atrophy score were also calculated for each group created with the 33rd percentile cut-offs (Normal-like, AD-like, MD-like, and VaD-like). Two sets of groups were created, one using hippocampal volume and WMH load, and the other using AD Atrophy score and WMH load.

Each group was then broken down by ultimate diagnosis in the memory clinic. Only participants that had a diagnosis listed in their electronic health record (including 'no diagnosis', such as 'Persons encountering health services for examination and investigation') were included in this portion of the analysis (N=334).

5.3 RESULTS

5.3.1 Demographics and Imaging Analyses

Average age, MMSE score, WMH load, normalised hippocampal volume and AD Atrophy score were calculated for each diagnostic category (Table 5-8). To test for differences between diagnostic groups a one-way ANOVA was run with Bonferroni post-hoc tests. Because of the large number of contrasts, this is included in appendix 4.

Table 5-8 – *Number of participants (N) and average age, MMSE, WMH load (measured in mL), normalised hippocampal volume, and AD Atrophy score for each diagnostic category. Age, MMSE, WMH Load, normalised hippocampal volume, and AD Atrophy score all = Mean (Standard Deviation). * Denotes equal group differences at p < 0.001 significance, Bonferroni post-hoc tests can be found in appendix 3. ** Average hippocampal values based on participants who had MMSE score available (N=428).*

	N	Age *	MMSE *,**	WMH Load *	Normalised HC volume *	AD Atrophy score *
Diagnosis Not Listed	255	71.82 (11.28)	25.88 (3.57)	9.73 (12.99)	0.00218 (0.000476)	0.401 (0.382)
No Diagnosis	13	73.54 (8.02)	26.46 (2.70)	13.85 (17.87)	0.00195 (0.000451)	0.580 (0.340)
Alzheimer's Disease	144	76.53 (7.73)	22.07 (4.97)	11.13 (10.34)	0.00191 (0.000363)	0.683 (0.340)
Mild Cognitive Impairment	51	74.86 (7.20)	26.59 (3.05)	10.07 (11.63)	0.00217 (0.000335)	0.356 (0.278)
Mixed Dementia	38	78.13 (7.12)	22.03 (4.76)	17.05 (13.22)	0.00190 (0.000335)	0.684 (0.299)
Vascular Dementia	17	76.47 (7.25)	20.76 (4.79)	24.46 (20.88)	0.00209 (0.000246)	0.419 (0.220)
Unspecified Dementia	21	74.19 (6.84)	20.67 (5.60)	11.26 (11.81)	0.00204 (0.000438)	0.554 (0.290)
Other Dementia	8	69.00 (9.06)	19.00 (7.35)	9.85 (12.41)	0.00220 (0.000239)	0.368 (0.397)
Other Psychiatric	42	68.5 (11.75)	24.07 (5.00)	9.70 (10.55)	0.00226 (0.000413)	0.353 (0.372)
Total	589	73.63 (9.97)	23.59 (4.96)	11.14 (12.76)	0.00209 (0.000436)	0.491 (0.374)

5.3.2 Cut-off 1 for discriminating 'low' and 'high' groups: Median Values

Furthermore, average age, MMSE score, WMH load, normalised hippocampal volume and AD Atrophy score were calculated for each cut off group created. Two separate sets of groups were created using this cut-off, one using hippocampal volume and WMH load and one using AD Atrophy score and WMH load.

5.3.2.1 Hippocampal Volume and WMH load

Average age, MMSE score, WMH load, normalised hippocampal volume and AD Atrophy score are listed for the groups based on hippocampal volume and WHM load below (Table 5-9). All measures

significantly differed between the groups, and complete ANOVA results with Bonferroni post-hoc test can be found in appendix 4.

Table 5-9 – *Each group created with Median value cut-offs (using hippocampal volume and WMH load): number of participants (N) and average age, MMSE, WMH load (measured in mL), normalised hippocampal volume, and AD Atrophy score for each diagnostic category. Age, MMSE, WMH Load, normalised hippocampal volume, and AD Atrophy score all = Mean (Standard Deviation). * Denotes equal group differences at p < 0.001 significance, Bonferroni post-hoc tests can be found in appendix 4. ** Average based on participants who had MMSE score available (N=428).*

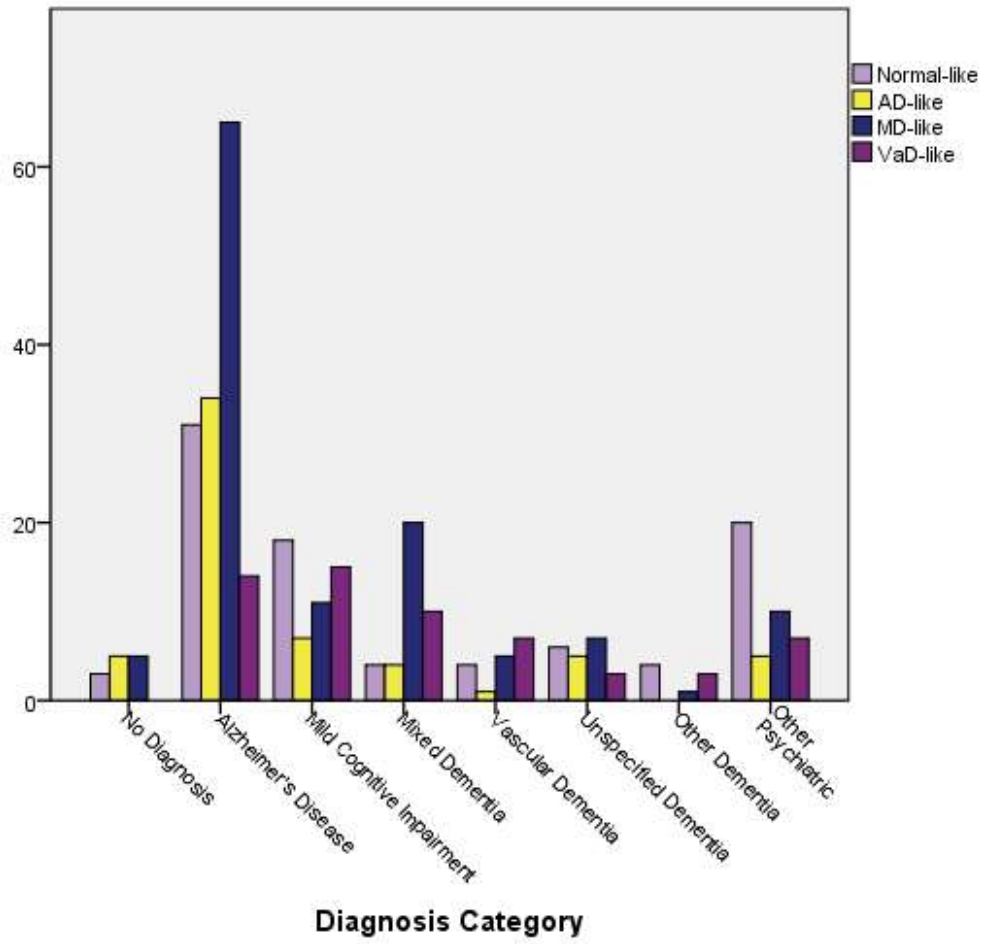
	N	Age *	MMSE *,**	WMH Load *	Normalised HC volume *	AD Atrophy score *
Normal-like	195	65.62 (10.22)	25.10 (4.30)	2.18 (1.94)	0.00252 (0.000299)	0.184 (0.301)
AD-like	100	74.66 (7.03)	23.46 (4.70)	3.37 (1.97)	0.00178 (0.000222)	0.699 (0.295)
MD-like	195	79.20 (6.38)	21.99 (5.15)	19.72 (12.97)	0.00172 (0.000229)	0.737 (0.275)
VaD-like	99	77.38 (7.40)	23.86 (5.14)	19.77 (13.76)	0.002283 (0.000177)	0.399 (0.248)

Using these cut-offs, groups were then broken down by their ultimate memory clinic diagnosis (Table 5-10) (Figure 5-1). Only those that had a diagnosis (including no diagnosis, such as 'Persons encountering health services for examination and investigation') in their electronic health record was included in this analysis (N=334). Out of the 334 participants with a diagnosis 90 participants were classified as normal-like, 61 were classified as AD-like, 124 were classified as MD-like, and 59 were classified as VaD-like using the median normalised hippocampal volume and WMH load as cut-offs.

Table 5-10 – *Groups (based on hippocampal volume and white matter hyperintensity load) broken down by Memory Clinic diagnosis, only including those patients with a final diagnosis (N=334). Median values used as cut-offs.*

		No Diagnosis	Alzheimer's Disease	Mild Cognitive Impairment	Mixed Dementia	Vascular Dementia	Unspecified Dementia	Other Dementia	Other Psychiatric Condition	Total
Normal-like	Count	3	31	18	4	4	6	4	20	90
	% within group	3.3%	34.4%	20.0%	4.4%	4.4%	6.7%	4.4%	22.2%	100.0%
	% within Diagnosis Category	23.1%	21.5%	35.3%	10.5%	23.5%	28.6%	50.0%	47.6%	26.9%
AD-like	Count	5	34	7	4	1	5	0	5	61
	% within group	8.2%	55.7%	11.5%	6.6%	1.6%	8.2%	0.0%	8.2%	100.0%
	% within Diagnosis Category	38.5%	23.6%	13.7%	10.5%	5.9%	23.8%	0.0%	11.9%	18.3%
MD-like	Count	5	65	11	20	5	7	1	10	124
	% within group	4.0%	52.4%	8.9%	16.1%	4.0%	5.6%	0.8%	8.1%	100.0%
	% within Diagnosis Category	38.5%	45.1%	21.6%	52.6%	29.4%	33.3%	12.5%	23.8%	37.1%
VaD-like	Count	0	14	15	10	7	3	3	7	59
	% within group	0.0%	23.7%	25.4%	16.9%	11.9%	5.1%	5.1%	11.9%	100%
	% within Diagnosis Category	0.0%	9.7%	29.4%	26.3%	41.2%	14.3%	37.5%	16.7%	17.7%
Total	Count	13	144	51	38	17	21	8	42	334
	% within group	3.9%	43.1%	15.3%	11.4%	5.1%	6.3%	2.4%	12.6%	100%
	% within Diagnosis Category	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100%

Figure 5-1 *– Number of patients in each diagnostic category. Median values (based on hippocampal volume and white matter hyperintensity load) used as cut-offs.*



Within the 61 subjects that were classified as AD-like, 34 (55.7%) received a diagnosis of AD from the memory clinic. For the 124 subjects that were classified as MD-like, only 20 (16.1%) received a diagnosis of MD, while 65 (52.4%) received a diagnosis of AD. The VaD group was the smallest, with only 59 subjects. Of these 59 subjects, only 7 (11.9%) were given a diagnosis of VaD, while 14 (23.7%) received a diagnosis of AD and 10 (16.9%) received a diagnosis of MD.

When looking at subjects based on diagnosis, only 34 of the 144 (23.6%) subjects that received a diagnosis of AD were categorised as having an AD-like brain. The largest portion of patients who received a diagnosis of AD were categorised as MD-like (45.1%).

5.3.2.2 AD Atrophy score and WMH load

Average age, MMSE score, WMH load, hippocampal volume and AD Atrophy score are listed for the group based on AD Atrophy score and WHM load below (Table 5-11). All measures significantly differed between the groups, and complete ANOVA results with Bonferroni post-hoc test can be found in appendix 5.

***Table 5-11** – Each group created with Median value cut-offs (using AD Atrophy score and WMH load): number of participants (N) and average age, MMSE, WMH load (measured in mL), normalised hippocampal volume, and AD Atrophy score for each diagnostic category. Age, MMSE, WMH Load, normalised hippocampal volume, and AD Atrophy score all = Mean (Standard Deviation). * Denotes equal group differences at p < 0.001 significance, Bonferroni post-hoc tests can be found in appendix 5. ** Average based on participants who had MMSE score available (N=428).*

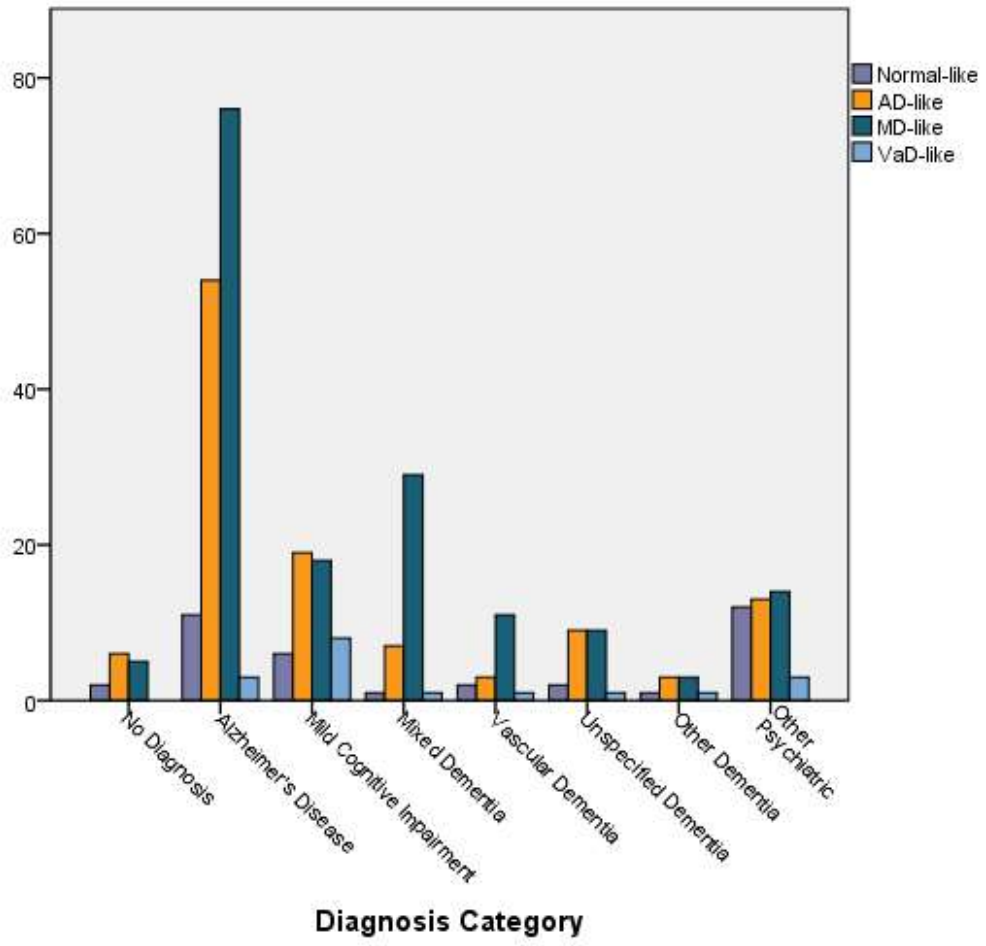
	N	Age *	MMSE *,**	WMH Load *	Normalised HC volume *	AD Atrophy score *
Normal-like	110	61.17 (8.93)	26.42 (3.26)	1.43 (1.63)	0.00264 (0.000311)	-0.030 (0.166)
AD-like	185	73.15 (8.06)	23.47 (4.76)	3.266 (1.93)	0.00205 (0.000361)	0.592 (0.272)
MD-like	266	79.06 (6.59)	22.07 (5.23)	19.71 (13.20)	0.00187 (0.000322)	0.6825 (0.260)
VaD-like	28	74.11 (7.06)	26.92 (2.36)	19.93 (13.65)	0.00230 (0.000271)	0.0619 (0.123)

Groups were once again broken down by diagnostic category (Table 5-12) (Figure 5-2). Only those that had a diagnosis (including no diagnosis, such as 'Persons encountering health services for examination and investigation') in their electronic health record was included in this analysis (N=334). Using AD Atrophy score instead of normalised hippocampal volume significantly changed distribution of subjects across groups. With these variables, only 37 subjects were classified as normal-like, 114 were classified as AD-like, 165 were classified as MD-like, and only 18 subjects were classified as VaD-like.

Table 5-12 *- Groups (based on AD Atrophy score and white matter hyperintensity load) broken down by Memory Clinic diagnosis. Median values used as cut-offs.*

		No Diagnosis	Alzheimer's Disease	Mild Cognitive Impairment	Mixed Dementia	Vascular Dementia	Unspecified Dementia	Other Dementia	Other Psychiatric Condition	Total
Normal-like	Count	2	11	6	1	2	2	1	12	37
	% within group	5.4%	29.7%	16.2%	2.7%	5.4%	5.4%	2.7%	32.4%	100%
	% within Diagnosis Category	15.4%	7.6%	11.8%	2.6%	11.8%	9.5%	12.5%	28.6%	11.1%
AD-like	Count	6	54	19	7	3	9	3	13	114
	% within group	5.3%	47.4%	16.7%	6.1%	2.6%	7.9%	2.6%	11.4%	100%
	% within Diagnosis Category	46.2%	37.5%	37.3%	18.4%	17.6%	42.9%	37.5%	31.0%	34.1%
MD-like	Count	5	76	18	29	11	9	3	14	165
	% within group	3.0%	46.1%	10.9%	17.6%	6.7%	5.5%	1.8%	8.5%	100%
	% within Diagnosis Category	38.5%	52.8%	35.3%	76.3%	64.7%	42.9%	37.5%	33.3%	49.4%
VaD-like	Count	0	3	8	1	1	1	1	3	18
	% within group	0.0%	16.7%	44.4%	5.6%	5.6%	5.6%	5.6%	16.7%	100%
	% within Diagnosis Category	0.0%	2.1%	15.7%	2.6%	5.9%	4.8%	12.5%	7.1%	5.4%
Total	Count	13	144	51	38	17	21	8	42	334
	% within group	3.9%	43.1%	15.3%	11.4%	5.1%	6.3%	2.4%	12.6%	100%
	% within Diagnosis Category	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100%

Figure 5-2 *– Number of patients in each diagnostic category. Median values (based on AD Atrophy score and white matter hyperintensity load) used as cut-offs.*



For those categorised as AD-like, 54 (47.4%) went on to receive a diagnosis of AD, and 19 (16.7%) received a diagnosis of MCI. Those categorised as MD-like were mostly diagnosed with AD (46.1%), with only 17.6% receiving a diagnosis of MD. Those categorised as VaD-like were most likely to receive a diagnosis of MCI (44.4%).

52.8% of patients who received a final diagnosis of AD were categorised as MD-like, while 37.5% were classified as AD-like. Out of the 17 people who were ultimately diagnosed with VaD, 11 (64.7%) were classified as MD-like and only one was classified as VaD-like.

5.3.3 Cut-off 2 for discriminating 'low' and 'high' groups: 33rd Percentiles

Averages were calculated for each cut off group created. Two separate sets of groups were created using this cut-off, one using hippocampal volume and WMH load and one using AD Atrophy score and WMH load.

5.3.3.1 Hippocampal Volume and WMH load

Average age, MMSE score, WMH load, hippocampal volume and AD Atrophy score are listed for the groups based on hippocampal volume and WHM load below (Table 5-13). All measures significantly differed between the groups, and complete ANOVA results with Bonferroni post-hoc test can be found in appendix 6.

Table 5-13 – *Each group created with 33rd percentile cut-offs (using hippocampal volume and WMH load): number of participants (N) and average age, MMSE, WMH load (measured in mL), normalised hippocampal volume, and AD Atrophy score for each diagnostic category. Age, MMSE, WMH Load, normalised hippocampal volume, and AD Atrophy score all = Mean (Standard Deviation). * Denotes equal group differences at p < 0.001 significance, Bonferroni post-hoc tests can be found in appendix 6. ** Average based on participants who had MMSE score available (N=428).*

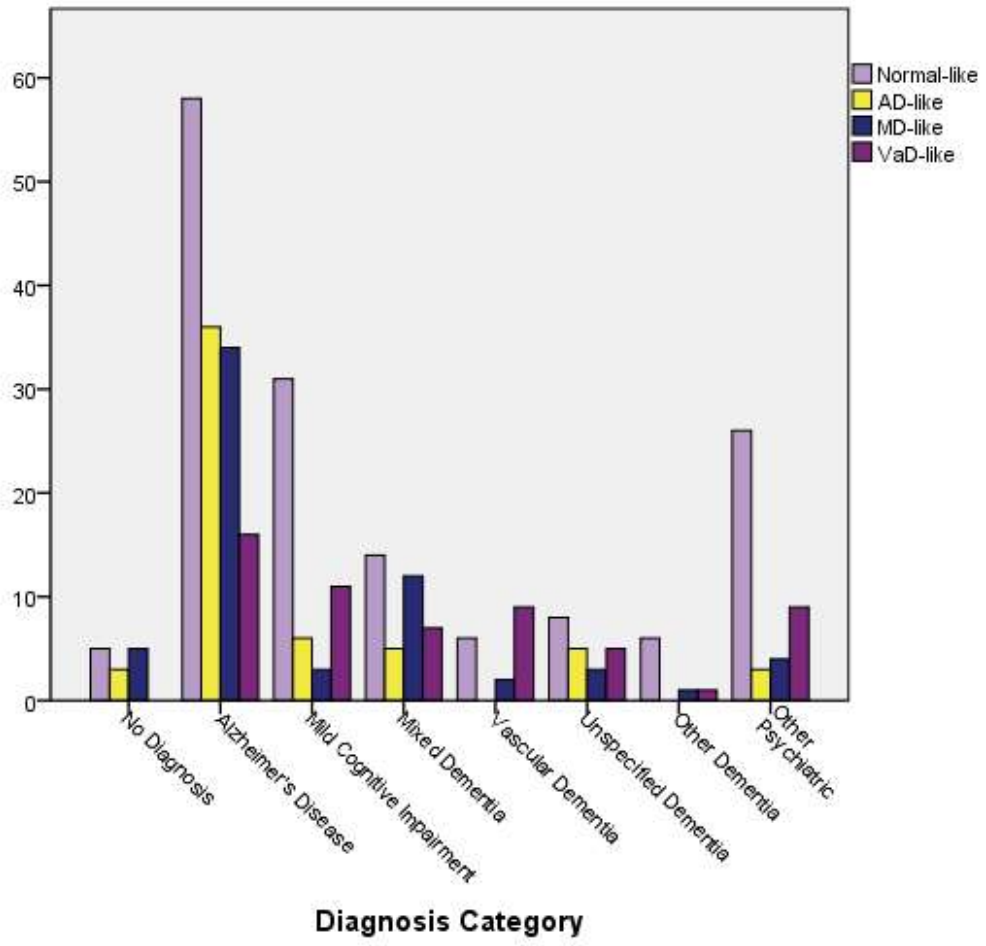
	N	Age *	MMSE *,**	WMH Load *	Normalised HC volume *	AD Atrophy score *
Normal-like	296	69.09 (10.51)	24.81 (4.10)	3.75 (3.32)	0.00238 (0.000334)	0.292 (0.335)
AD-like	97	76.67 (7.12)	22.96 (4.92)	5.45 (3.11)	0.00165 (0.000183)	0.787 (0.276)
MD-like	99	79.49 (6.64)	21.60 (5.28)	25.22 (13.47)	0.00160 (0.000189)	0.813 (0.264)
VaD-like	97	78.43 (6.48)	22.36 (6.10)	25.042 (12.95)	0.00214 (0.000194)	0.471 (0.216)

Groups were once again broken down by diagnostic category (Table 5-14) (Figure 5-3). Only those that had a diagnosis in their electronic health record (including no diagnosis, such as 'Persons encountering health services for examination and investigation') was included in this analysis (N=334). These more stringent cut-offs created a significantly larger control-like group (154). 58 subjects were classified as AD-like, 64 were classified as MD-like, and the final 58 were classified as VaD-like.

Table 5-14 – *Groups (based on hippocampal volume and white matter hyperintensity load) broken down by Memory Clinic diagnosis. 33rd percentiles used as cut-offs.*

		No Diagnosis	Alzheimer's Disease	Mild Cognitive Impairment	Mixed Dementia	Vascular Dementia	Unspecified Dementia	Other Dementia	Other Psychiatric Condition	Total
Normal-like	Count	5	58	31	14	6	8	6	26	154
	% within group	3.2%	37.7%	20.1%	9.1%	3.9%	5.2%	3.9%	16.9%	100%
	% within Diagnosis Category	38.5%	40.3%	60.8%	36.8%	35.3%	38.1%	75.0%	61.9%	46.1%
AD-like	Count	3	36	6	5	0	5	0	3	58
	% within group	5.2%	62.1%	10.3%	8.6%	0.0%	8.6%	0.0%	5.2%	100%
	% within Diagnosis Category	23.1%	25.0%	11.8%	13.2%	0.0%	23.8%	0.0%	7.1%	17.4%
MD-like	Count	5	34	3	12	2	3	1	4	64
	% within group	7.8%	53.1%	4.7%	18.8%	3.1%	4.7%	1.6%	6.3%	100%
	% within Diagnosis Category	38.5%	23.6%	5.9%	31.6%	11.8%	14.3%	12.5%	9.5%	19.2%
VaD-like	Count	0	16	11	7	9	5	1	9	58
	% within group	0.0%	27.6%	19.0%	12.1%	15.5%	8.6%	1.7%	15.5%	100%
	% within Diagnosis Category	0.0%	11.1%	21.6%	18.4%	52.9%	23.8%	12.5%	21.4%	17.4%
Total	Count	13	144	51	38	17	21	8	42	334
	% within group	3.9%	43.1%	15.3%	11.4%	5.1%	6.3%	2.4%	12.6%	100%
	% within Diagnosis Category	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100%

Figure 5-3 – *Number of patients in each diagnostic category. 33rd percentile values (based on hippocampal volume and white matter hyperintensity load) used as cut-offs.*



The normal-like category saw the greatest increase in diagnostic categories, with 58 (37.7%) being diagnosed with AD, 31 (20.1%) being diagnosed with MCI, 11 (9.1%) being diagnosed with MD, and 6 (3.9%) being diagnosed with VaD.

A large portion of MD-like subjects received a diagnosis of AD (53.1%), while only 12 (18.8%) received a diagnosis of MD. Additionally, 27.6% of VaD-like subjects received a diagnosis of AD. Out of the 58 VaD-like subjects, 11 (19%) received a diagnosis of MCI, 12 (18.8%) received a diagnosis of MD, and 9 (15.5%) received a diagnosis of VaD.

5.3.3.2 AD Atrophy score and WMH load

Average age, MMSE score, WMH load, hippocampal volume and AD Atrophy score are listed for the group based on AD Atrophy score and WHM load below (Table 5-15). All measures significantly differed between the groups, and complete ANOVA results with Bonferroni post-hoc test can be found in appendix 7.

Table 5-15 *- Each group created with 33rd percentile cut-offs (using AD Atrophy score and WMH load): number of participants (N) and average age, MMSE, WMH load (measured in mL), normalised hippocampal volume, and AD Atrophy score for each diagnostic category. Age, MMSE, WMH Load, normalised hippocampal volume, and AD Atrophy score all = Mean (Standard Deviation). * Denotes equal group differences at p < 0.001 significance, Bonferroni post-hoc tests can be found in appendix 6. ** Average based on participants who had MMSE score available (N=428).*

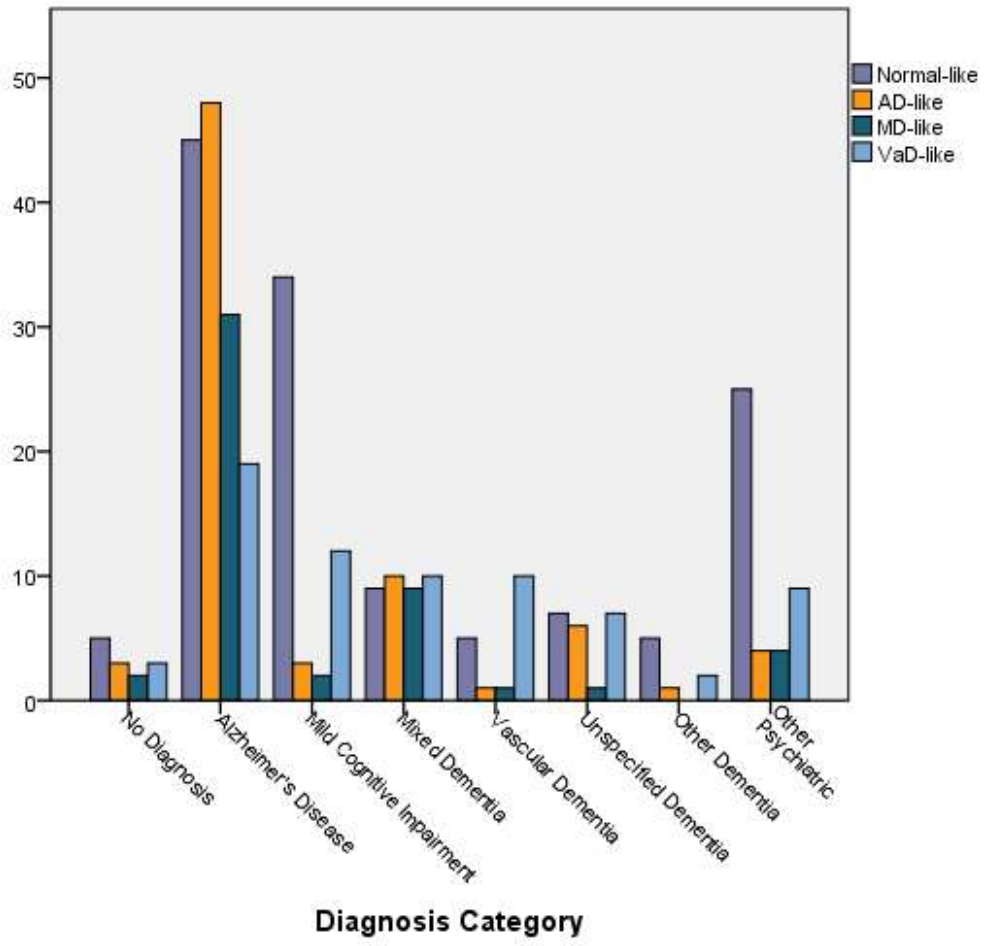
	N	Age *	MMSE *,**	WMH Load *	Normalised HC volume *	AD Atrophy score *
Normal-like	282	68.67 (10.28)	25.24 (3.67)	3.68 (3.32)	0.00236 (0.000388)	0.229 (0.271)
AD-like	110	76.79 (7.86)	22.28 (5.19)	5.39 (3.08)	0.00179 (0.000267)	0.884 (0.177)
MD-like	85	79.44 (6.54)	19.81 (5.68)	24.14 (12.50)	0.00168 (0.000282)	0.909 (0.193)
VaD-like	111	78.61 (6.59)	23.57 (5.15)	25.89 (13.69)	0.00209 (0.000303)	0.441 (0.175)

Groups were once again broken down by diagnostic category (Table 5-16) (Figure 5-4). Only those that had a diagnosis (including no diagnosis, such as 'Persons encountering health services for examination and investigation') in their electronic health record was included in this analysis (N=334). Once again, using the 33rd percentile cut-offs created a larger normal-like group than the median cut-offs. A total of 135 subjects were classified as normal-like, while 77 were classified as AD-like, 50 were classified as MD-like, and 72 were classified as VaD-like.

Table 5-16 – *Groups (based on AD Atrophy score and white matter hyperintensity load) broken down by Memory Clinic diagnosis. 33rd percentiles used as cut-offs.*

		No Diagnosis	Alzheimer's Disease	Mild Cognitive Impairment	Mixed Dementia	Vascular Dementia	Unspecified Dementia	Other Dementia	Other Psychiatric Condition	Total
Normal -like	Count	5	45	34	9	5	7	5	25	135
	% within groups	3.7%	33.3%	25.2%	6.7%	3.7%	5.2%	3.7%	18.5%	100%
	% within Diagnosis Category	38.5%	31.3%	66.7%	23.7%	29.4%	33.3%	62.5%	59.5%	40.4%
AD-like	Count	3	49	3	10	1	6	1	4	77
	% within groups	3.9%	63.6%	3.9%	13.0%	1.3%	7.8%	1.3%	5.2%	100%
	% within Diagnosis Category	23.1%	34.0%	5.9%	26.3%	5.9%	28.6%	12.5%	9.5%	23.1%
MD-like	Count	2	31	2	9	1	1	0	4	50
	% within groups	4.0%	62.0%	4.0%	18.0%	2.0%	2.0%	0.0%	8.0%	100%
	% within Diagnosis Category	15.4%	21.5%	3.9%	23.7%	5.9%	4.8%	0.0%	9.5%	15.0%
VaD-like	Count	3	19	12	10	10	7	2	9	72
	% within groups	4.2%	26.4%	16.7%	13.9%	13.9%	9.7%	2.8%	12.5%	100%
	% within Diagnosis Category	23.1%	13.2%	23.5%	26.3%	58.8%	33.3%	25.0%	21.4%	21.6%
Total	Count	13	144	51	38	17	21	8	42	334
	% within groups	3.9%	43.1%	15.3%	11.4%	5.1%	6.3%	2.4%	12.6%	100%
	% within Diagnosis Category	100.0%	100.0%	100.0%	100.0%	100.0%	100.00%	100.00%	100.0%	100%

Figure 5-4 – *Number of patients in each diagnostic category. 33rd percentile values (based on AD Atrophy score and white matter hyperintensity load) used as cut-offs.*



The majority of subjects who were classified as normal-like were diagnosed with AD (33.3%) or MCI (25.2%).

Most subjects who were classified as AD-like were further diagnosed with AD (63.6%), with a small portion being diagnosed with MD (13%). While this cut-off and variable combination produced the least number of subjects classified as MD, out of the 50 subjects that were classified as such 31 (62%) were diagnosed with AD. VaD patients were mostly diagnosed with AD (26.4%) or MCI (16.7%), while MD and VaD had the same percentage of subjects (13.9%)

The subjects who received a diagnosis of MD were evenly split across the four group types (AD and VaD-like 26.3%; Normal and MD like 23.7%).

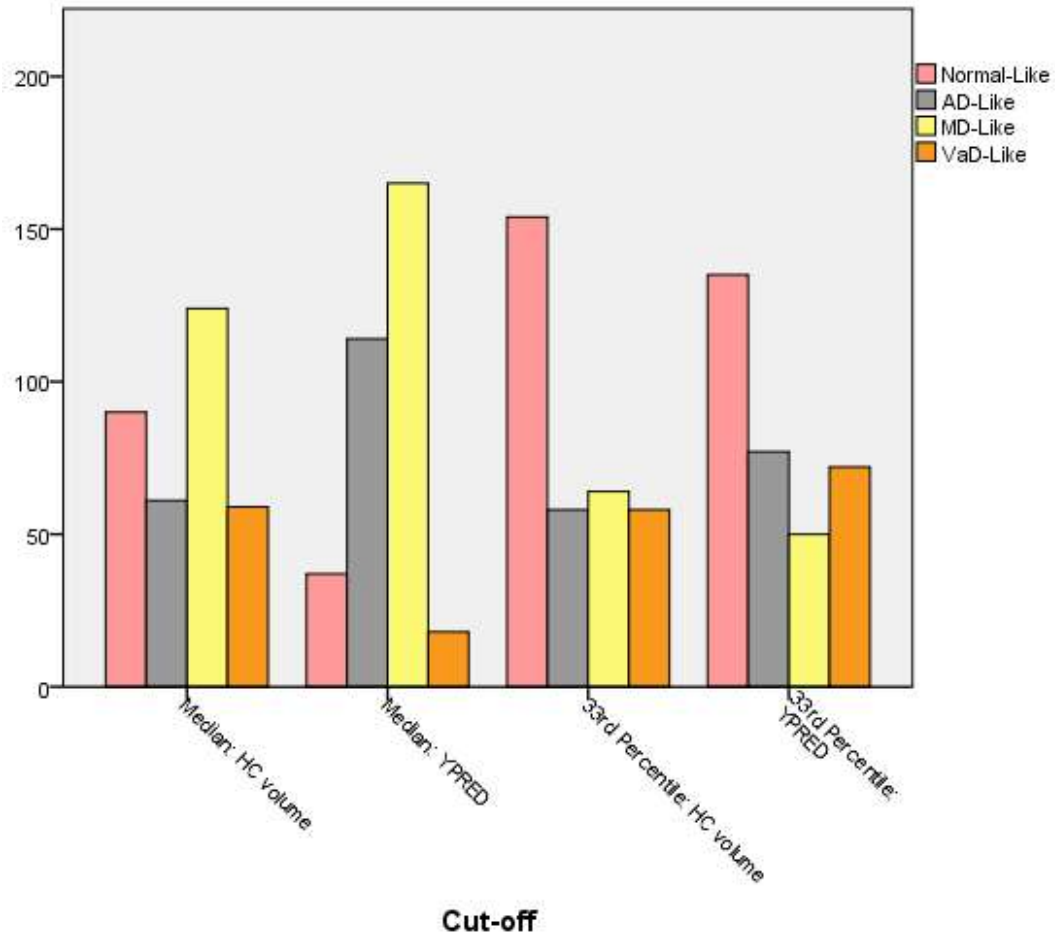
5.4 Discussion

Patients of the memory clinic cohort were all classified into one of four categories based on measures of AD (hippocampal atrophy or AD Atrophy score) and VaD pathology (WMH). These categories are only theoretical. There is more crossover between the disorders than accounted for with only four categories, as all patients fall somewhere on a continuum. Additionally, the use of strict cut-offs does not take into account the heterogeneity of disorders, and the fact that there is a continuum. Both time (early versus late stage of the disease) and severity of a given pathology influences where a patient will fall on the disease continuum. This was only the first step in investigating the use of cut-offs for these variables of interest, and gave some insight into the potential underdiagnosis of MD in a memory clinic cohort.

Those who had hippocampal little atrophy or an AD Atrophy score closer to 0 (what is considered control-like) and little WMH as measured by automated methods were categorised as normal-like. Those who had high hippocampal atrophy or an AD Atrophy score closer to 1 (what is considered AD-like) and little WMH were categorised as AD-like. Patients that had little hippocampal atrophy or an AD Atrophy score closer to normal, with a large amount of WMH were categorised as VaD-like. Finally, those who had severe hippocampal atrophy or an AD Atrophy score indicative of AD, and a large amount of WMH were categorised as MD-like.

The difference in group distribution over the various cut-offs can be seen in figure 5-5.

Figure 5-5 – *Number of patients in each group category (Normal-like, AD-like, MD-like, and VaD-like), based on the various cut-off values and variables of interest used.*



5.4.1 Imaging Results for Diagnostic Categories

As expected, those with a final diagnosis of AD or MD had the lowest hippocampal volumes across the diagnostic categories (0.00191 and 0.00190 respectively) (Table 5-8). Additionally, they had the highest AD atrophy scores (0.683 and 0.684 respectively). AD and MD are expected have similar scores, as both disorders exhibit the quintessential neuropathologies of AD. Furthermore, those with a final diagnosis of VaD had the largest amount of WMH (27.46 mL), followed by those with a final diagnosis of MD (17.05 mL). AD had a greater amount of WHM (11.13 mL) than MCI and other psychiatric disorder, further supporting that AD experiences more WMH than those without a form of dementia (Barber et al., 1999).

Interestingly, AD did not have more WMH than those with no diagnosis. However, it is important to remember that even though these patients did not have a final diagnosis, they are still not to be considered healthy controls. The no diagnosis group did have a much higher MMSE score, indicating their cognitive decline may be related to a disorder other than dementia.

5.4.2 Cut-off 1 for discriminating 'low' and 'high' groups: Median Values

The first group cut-off used in this study was based on the median value of each variable of interest for the memory clinic cohort (Table 5-2). While this may seem arbitrary, there are several studies that have used this approach when grouping subjects in a similar matter, such as high and low white matter load groups (Eckerström et al., 2011; Mortamais et al., 2014; Tuladhar et al., 2015). In this memory clinic cohort, the median value was quite close to what previous studies have found to be the average WMH load in healthy, age-matched adults plus one standard deviation (Benedictus et al., 2014; Gattringer et al., 2012; Maillard et al., 2012). This method of using mean plus one standard deviation has also been used in other studies looking at WMH burden in a dementia population (E. E. Smith et al., 2008). Additionally, the median normalised hippocampal volume is also close to the mean value, minus one standard deviation seen in the healthy control subset of the ADNI cohort used in the training set of the OPLS analysis in Chapter 4: OPLS analysis in a Memory Clinic Cohort (for full analysis, see appendix 8). Average normalised hippocampal volumes of healthy older adults can be challenging to find in the literature, as a result of the abundance of normalisation methods. Lastly, the AD Atrophy score median is very close to the 0.5 cut-off traditionally used in OPLS studies (Westman, Cavallin, Muehlboeck, et al., 2011a; Westman, Simmons, Muehlboeck, et al., 2011; Westman, Simmons, Zhang, et al., 2011; Westman et al., 2013).

5.4.2.1 Using Hippocampal Volume as a Measure of AD pathology

As expected, a large portion of subjects classified as AD-like using hippocampal volume and WMH were ultimately diagnosed with AD (55.7%). Interestingly, 52.4% of subjects classified as MD-like also received a diagnosis of AD and only 16.1% of these subjects received a diagnosis of MD.

When looking at subjects classified as VaD-like, 23.7% had a diagnosis of AD, 25.4% had a diagnosis of MCI, and 16.9% received a diagnosis of MD. Only 11.9% of subjects categorised as VaD-like actually went on to receive a diagnosis of VaD. It has been suggested that the absence of MRI exams could lead to the overdiagnosis of AD, and the underdiagnosis of VaD (Caixeta, Soares, & Soares, 2009). While everyone in this cohort received MRI examination, there may be other factors at play and may reflect a different bias to over-diagnose AD.

5.4.2.2 Using an AD Atrophy score as a Measure of AD pathology

Using AD Atrophy score, there were more subjects classified as AD-like overall compared to the use of hippocampal volume (114 vs 61 respectively), however the increase in AD-like patients was not only seen in those with an AD diagnosis, but in all diagnostic categories. 47.4% of those categorised as AD-like received a diagnosis of AD.

Of those who did receive a diagnosis of AD, 37.5% were categorised as AD-like, which is a larger percentage than using hippocampal volume as a measure of AD pathology (23.6%). 52.8% of those with an AD diagnosis were classified as MD-like.

Additionally, out of those diagnosed with VaD, 64.7% were classified as MD-like. Using an AD Atrophy score score with the median value cut-off, 49.4% of subjects were classified as MD-like. This suggests a median cut-off may not be effective at distinguishing AD and VaD, and is instead grouping these patients as MD-like.

5.4.3 Cut-off 2 for discriminating 'low' and 'high' groups: 33rd percentiles

While means plus one standard deviation may be a good cut-off for distinguishing healthy controls from patients, it does not take into account the variability within disorders. AD patients seem to have significantly more WHM than healthy controls, and studies have seen this WMH volume to be on average somewhere between 7 and 10 mL (Benedictus et al., 2014; Maillard et al., 2012). Using the previous median cut-off of 6.99, AD patients may be wrongly classified as MD-like. Similarly, VaD patients have hippocampi that are significantly larger than those of AD patients, but significantly smaller than healthy controls (Kim et al., 2015). To take into account these differences from healthy controls, the memory clinic was divided into three (33rd percentiles). We then only used the lowest third (33rd percentile) for HC volume, and the very highest third (66th percentile) for WHM load and AD Atrophy score (Table 5-5).

These new cut-offs may be more representative of the actual underlying pathologies. A cut-off of 11.62 mL for WMH instead of 6.99 will now take into account those AD patients with higher WHM load. The lowest third for hippocampal volume will now factor in those VaD patients that have smaller hippocampi. This is likely the reason that the MD-like group had the largest number in both (hippocampal volume and AD Atrophy score) median cut-offs.

The 33rd percentile cut-off redistributed roughly half of the patients previously classified as MD-like, and there was a more equal distribution of AD-like and VaD-like subjects compared to using median values as a cut-off. This indicates the new cut-off may be better at distinguishing AD and VaD. It does not classify AD subjects as MD-like because there more WMH than normal that is actually due to AD, and does not classify VaD subjects as MD-like because of a slightly smaller than normal hippocampal volume due to VaD.

Conversely, these stricter cut-offs may not take into consideration the variation within the disorders, and that there is a continuum of symptom severity. Using the 33rd percentile cut-offs nearly doubled the number of subjects classified as normal-like. As this is a memory clinic, with no truly healthy controls, it does not make sense that the largest classification group would be normal-like. The previous chapter (*Chapter 4: OPLS in a Memory Clinic Cohort*) discussed the most reliable cut-off for AD Atrophy score to distinguish between healthy controls and AD patients (*section 4.3.3.1*, *section 4.3.3.2*, and *section 4.4.3*). It was discussed that because the heterogeneity of AD pathology, a lower cut-off of 0.39 would better reflect this (D. Ferreira et al., 2015; Lam et al., 2013; Noh et al., 2014; Pereira et al., 2014b). When looking at AD Atrophy score alone, a cut-off of 0.34-0.39 may be better for distinguishing between AD and healthy controls, but 0.6-0.7 may be better for distinguishing between AD and VaD patients.

5.4.3.1 Using Hippocampal Volume as a Measure of AD pathology

In those with a final diagnosis AD, roughly the same number of patients were categorised as AD-like and MD-like (25% and 23.6% respectively), and a large portion were categorised as normal-like (40.3%). Despite the significantly stricter cut-off, 53.1% of patients categorised as MD-like were diagnosed with AD and only 18.8% were given a final diagnosis MD, suggesting there may be an underdiagnosis of MD.

5.4.3.2 Using AD Atrophy score as a Measure of AD pathology

Using AD Atrophy score score with 33rd percentile is the only cut-off group that created less MD-like than AD and VaD-like. Even then, out of those with categorised ad MD-like 62% were diagnosed with AD and only 18% were diagnosed with MD, further suggesting the underdiagnosis of MD. In those with VaD-like brains, 26.4% were diagnosed as AD, and 13.9% diagnosed as VaD (and another 13.9% diagnosed as MD), which may point to a fundamental overdiagnosis in AD across the memory clinic.

5.4.4 Hippocampal Volume versus AD atrophy score as a Measure of AD Pathology

For both cut-offs, AD Atrophy score categorised less subjects as normal-like than hippocampal volume did. This may be because of the more comprehensive nature of the OPLS analysis, where many subcortical structures and cortical thicknesses are taken into account when creating a score. Furthermore, AD is a heterogenous disorder, and some experience hippocampal-sparing forms of the disease (Daniel Ferreira, Verhagen, et al., 2017). Additionally, AD Atrophy score was heavily influenced by which cut-off was used, whereas using hippocampal volume created groups with similar numbers of AD-like and VaD-like patients, regardless of which cut-off was used.

5.4.5 Underdiagnosis of MD

Regardless of cut-off and variables used, there was a trend of patients classified as MD-like mostly receiving a diagnosis of AD. Because this was also the case even using the 33rd percentile with AD Atrophy score, which classified a much smaller portion of patients as MD-like (only 15%), there may be a fundamental underdiagnosis of MD or overdiagnosis of AD. It may also be the case that there may be a need for volumetric measures of WMH in addition to the current unstructured and structured radiological reporting, as it could eliminate ceiling effects seen in the use of visual rating scales (Mäntylä et al., 1997; Xiong & Mok, 2011).

There is strong evidence that WHM correlates with cognition in AD (Bilello et al., 2015; Oppedal et al., 2012) and in the healthy old (Fiford et al., 2017; Valdés Hernández et al., 2013). In MCI patients, hippocampal atrophy is correlated with white matter lesion load (Eckerström et al., 2011; Fiford et al., 2017). Others have found this relationship between WMH and grey matter atrophy are only present when looking at total brain cortical grey matter, suggesting VaD and AD pathologies effect cortical atrophy differently (Du et al., 2005). Taken together, the need to consider white matter changes in all forms of dementia is clear.

There is evidence suggesting the treatment of vascular risk factors can influence the rate of decline in AD (Valenti, Pantoni, & Markus, 2014). In the underdiagnosis of MD and overdiagnosis of AD there is a lack of addressing the vascular changes, and this may influence patient care.

Additionally, hippocampal atrophy but not white matter changes, predict cognitive changes in response of cholinesterase inhibitors (Cheng et al., 2015). MD presents with similar cholinergic deficiencies as AD, and these patients also seem to benefit from cholinesterase inhibitors (Perry, Ziabreva, Perry, Aarsland, & Ballard, 2005). While in the current study no underdiagnosis of MD due to an overdiagnosis of VaD was seen, it is important to note it is possible and could result in patients not receiving appropriate treatments.

5.4.6 Limitations

There are several limitations to this approach. As previously discussed, the median cut-off does not distinguish between AD and VaD well, whereas the stricter 33rd percentile cut-off creates an inaccurately large normal-like group. It may be that higher cut-offs are useful for defining strictly AD or strictly VaD, but the heterogeneity of the disorders results in lower cut-offs being more useful in defining disorders such as MCI or MD. It is plausible that while MD patients may not exhibit the same extent of neuropathological damage, they may be as severely cognitively impaired as those with AD or VaD because of the additive effects the individual pathologies have been seen to have on cognition (Snowdon et al., 1997).

There are various subtypes of AD and not all of them include hippocampal atrophy (Daniel Ferreira, Verhagen, et al., 2017). Because not all AD subtypes follow the typical pattern atrophy that can be measured with hippocampal volume or a AD Atrophy score that is based on the common medial temporal lobe focused AD, it may not be applicable to the entire population.

Additionally, as mentioned previously, these strict cut-offs do not consider the heterogeneity of disorders, and that patients lie somewhere on a continuum. Position on this continuum is undoubtedly influenced by both time (an early versus later stage of the disease) and severity of a given pathology influences where a patient will fall on the disease continuum.

5.4.6.1 Clinical Data

These assessments are purely based on imaging data, and do not take clinical information into account. It may be advantageous to take into consideration cardio vascular risk factors, as they can significantly contribute to the further development of various subtypes of VaD and potentially even AD (O'Brien & Thomas, 2015b).

Additionally, while MMSE was available and analysed when looking at group differences, it was not taken into account when categorising subjects. Neuropathologies of AD and VaD both influence cognitive ability, but they do so independently and may have an additive effect (Snowdon et al., 1997). Regardless of cut-off used, the MD-like group always had the lowest MMSE score compared to the other groups, which may be reflecting this additive effect. It may be useful to take MMSE score into consideration when grouping individuals, as it makes sense those with MD would have the lowest scores.

5.4.6.2 White Matter Lesions

As previously mentioned, VaD and VCI are extremely heterogenous, with a variety of causes (Hunt et al., 1989; Kurt A. Jellinger, 2008; O'Brien & Thomas, 2015b). Previous studies have found that different types of WM lesions correlate differently with cognition. Subcortical lesions seem to have a significant effect on cognition, while periventricular lesions do not (Stenset et al., 2008). Type of WMH was not taken into account in this analysis, and which may account for different diagnoses.

Additionally, as previously stated the LST toolbox was not designed for use in dementia patients. While it has been used previously to quantify WMH in patients with cognitive impairment, results may differ if the LST toolbox algorithm was trained on white matter lesions more specific to VaD and this must be taken into consideration when interpreting the results (Svärd et al., 2017).

5.4.6.3 Changes in Hippocampal Volume not due to Dementia

While hippocampal atrophy is a well-known marker of dementia and AD, these are not the sole causes. Studies have found volume differences can be dependent on Apolipoprotein E (APOE) in healthy controls and AD patients (Manning et al., 2014). Other psychiatric conditions, such as depression, are also related to hippocampal atrophy in older adults (Taylor et al., 2014). Genotypic data and comorbidities were not taken into account for this analysis, but may have influenced categorisation of subjects.

5.4.7 Future Directions

5.4.7.1 Cut-offs for MCI

Because the 33rd percentile was better suited for distinguishing between AD and VaD, but created too many normal-like controls, it would be interesting to create another set of cut-offs for MCI like individuals. This added category may give more insight to distribution of those experiencing symptoms, but do not yet have the pathology indicative of either AD, VaD, or MD.

5.4.7.2 Using Age-corrected AD Atrophy score values

There are global and regional brain changes that are thought to be related to healthy ageing in the absence of dementia that may negatively affect model performance in OPLS (*section 4.2.3.2.1*) (Dukart et al., 2011; Falahati et al., 2016). In the previous chapter, both age-corrected and age uncorrected models were created with the OPLS analysis (*section 4.2.3*). It may be better to use AD Atrophy score than hippocampal volume when creating such cut-offs, as the AD Atrophy score provides a more

comprehensive score of AD pathology in a patient. However, it would be interesting to regroup the subjects based on the age-corrected AD Atrophy score scores to see if that changes diagnostic category distribution.

5.4.7.3 OPLS

It would be possible to train the OPLS algorithm described in *Chapter 4: OPLS in a Memory Clinic Cohort* on different types of dementia instead of one type versus healthy controls. Creating a model that uses VaD and AD, instead of AD versus healthy controls, could create scores based on volumetric data and white matter hyperintensity and vascular data. Scores could then predict if someone was more AD or VaD like, or a middle score of 0.5 could suggest a diagnosis of MD.

5.5 CONCLUSION

Using imaging data, groups were created to identify the distribution of AD, VaD and MD pathology in memory clinic patients. Two different cut-off points were used, as well as two different variables to describe AD pathology. These cut-offs and grouping methods may be useful in a clinical setting with further research, however they are not robust enough currently. There is also substantial evidence supporting the hypothesis that MD is underdiagnosed in the clinic, and this is a problem that needs to be addressed. Automated WMH measurements may be an added tool for the assessment of MD.

6 BRAINMEASURE: AUTOMATED MORPHOMETRY FOR DEMENTIA DIAGNOSIS

6.1 INTRODUCTION

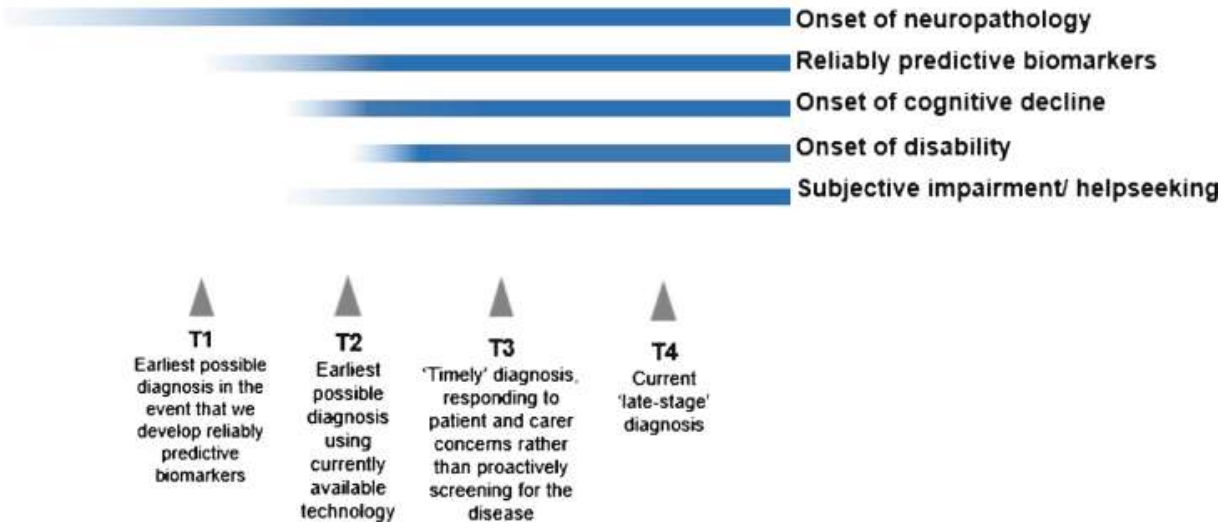
6.1.1 Current Clinical Diagnosis

Dementia is a growing problem. In the United Kingdom alone, roughly 850,00 people have some form of dementia, and this number is expected to grow to well over one million by the year 2025 (Alzheimer's Society, 2015). It is estimated that dementia costs the UK £26.3 billion a year, with that figure only expected to rise with the increase in cases (Alzheimer's Society, 2015).

Alarmingly, as of April of 2017 only 69.5% of people with dementia had a diagnosis ("Diagnoses in the UK," 2015). There is also a lack of specific diagnoses, such as Alzheimer's Disease (AD) or Vascular Dementia (VaD), which may contribute to the high cost of the disease as money is spent on follow-ups and repeat tests as the original diagnosis is unclear. For those who do receive a diagnosis, it is universally recognised that an earlier diagnosis is important both for patient experience and care, and from a public health perspective (G. M. McKhann et al., 2011; Samsi & Manthorpe, 2014; van Vliet et al., 2013). With the steady increase of diagnoses per year, there is also an increased burden on both primary care and memory clinics. Between 2008 and 2014 number of memory service users rose by 682% (Hodge & Hailey, 2015). This can be seen in increased time from referral to assessment (5.2 weeks in 2013 to 5.4 weeks in 2014) and increased time from assessment to diagnosis (8.4 weeks in 2013 to 8.6 weeks in 2014) (Hodge & Hailey, 2015). There are additional factors that may play into the time to diagnosis, such as early onset dementia taking significantly longer to diagnose than late onset dementia

(van Vliet et al., 2013). Earlier diagnoses should be achievable given AD's long prodromal stage (Figure 6-1).

***Figure 6-1** – Timeline of AD progression and diagnosis points on the disease continuum. From the Alzheimer's Disease International World Alzheimer Report 2011: The benefits of early diagnosis and intervention (M. Price, Bryce, & Ferri, 2011).*



6.1.1.1 Current use of Magnetic Resonance Imaging in Dementia Diagnoses

While current diagnostic criteria for AD focuses on clinical symptoms and evaluation, the National Institute for Health and Care Excellence (NICE) guidelines still recommend magnetic resonance imaging (MRI) scans, or computerised topography (CT) to rule out other brain disorders, unless the patient is presenting with moderate or severe dementia and the diagnosis is already clear (G. M. McKhann et al., 2011; National Collaborating Centre for Mental Health., 2007). It has been acknowledged that structural MRI can be invaluable to dementia and AD diagnoses, and its role in the diagnostic process is growing (Albert et al., 2011; G. M. McKhann et al., 2011; Sperling et al., 2011). However, many of the radiology reports obtained from brain imaging, especially in cases of early diagnosis, are often deemed inconclusive.

Currently memory clinics use MRI imaging in a variety of ways, from ruling out other disorders to visual rating scales (VRS) or more refined volumetric measurement methods. It is currently unclear exactly how many memory clinic patients receive any kind of brain scans, with some clinics referring nearly all patients and others referring only 40% (Burns, Wilkinson, & Peachey, 2014).

6.1.2 Study Rationale

It has been well established that there are a variety of benefits from timelier diagnoses of dementia, or one that is earlier than the current late stage diagnoses most often made. There is potentially great added value from earlier treatments and interventions. A timelier or earlier diagnosis, compared to one where symptoms are the moderate to severe stage, can allow patients and their families to better process the information about the disease, make any beneficial lifestyle changes, and more adequately plan for the future (Dubois, Padovani, Scheltens, Rossi, & Dell'Agnello, 2016). It may improve the overall quality of life for both the patient and the caregiver (Boise, Morgan, Kaye, & Camicioli, 1999; de Vugt & Verhey, 2013). Additionally, a timelier diagnosis may improve patient access to various support services and pathways of care, essentially making the disease more manageable (Dubois, Padovani, et al., 2016).

There have also been several studies considering the cost benefits associated with earlier diagnostic evaluation, with the assumption early interventions can hypothetically slow disease progression or delay institutionalisation. While these are still models based on assumptions, they show the potentially extraordinary cost benefits of an earlier diagnosis (Getsios, Blume, Ishak, Maclaine, & Hernández, 2012; Weimer & Sager, 2009).

While there a myriad of benefits to a timely diagnosis of AD, there are also a few potential challenges. There are potentially several ethical issues, including questions about competency before severe symptoms and potential discrimination and stigmatisation of patients (Lliffe & Manthorpe, 2004; Mattsson, Brax, & Zetterberg, 2010; Milne, 2010). Another major concern of earlier diagnoses is the

potential for a higher rate of misdiagnoses, that are either delayed, wrong, or completely diagnosis altogether. Misdiagnosis in general medical care create the potential for greater expense, and even patient harm (Gandhi et al., 2006; Graber, Franklin, & Gordon, 2005; Schiff et al., 2005; Singh, Naik, Rao, & Petersen, 2008). For AD and dementia more specifically, this could lead to a lost opportunity for treatment and both increased patient and carer burden (Bradford, Kunik, Schulz, Williams, & Singh, 2009). This is a problem that could also result in inappropriate treatments, including taking dementia medication when it is not needed or not getting correct therapy for something that is treatable (Gaugler et al., 2013).

Currently, clinical diagnoses have a sensitivity somewhere between 70.9% and 87.3% (Beach et al., 2012). There is clearly room for improvement, and it has been suggested that imaging biomarkers may be the way forward with more validation (G. M. McKhann et al., 2011). It has been well documented that volume changes in various areas of the brain are predictive of clinical changes in AD and dementia. While brain atrophy is normal in healthy ageing, it is significantly accelerated in dementia. A variety of studies have documented this, and one meta-analysis has found 2.2-fold higher volume loss in the hippocampus (HC), and a 1.8-fold higher volume loss in the whole brain in MCI patients, demonstrating just how marked the volumetry differences can be (Tabatabaei-Jafari, Shaw, & Cherbuin, 2015). There are a multitude of volume methods used in research based cohorts that show volumetry measures can aid in diagnosis and perhaps even predict conversion from MCI to AD (Cui et al., 2011; Cuingnet et al., 2011; Yawu Liu, Paajanen, Zhang, et al., 2010). While multivariate image analyses are better suited to this task, it seems that HC volumes can still do a reasonable prediction job on its own (Schmitter et al., 2015; Westman, Simmons, Zhang, et al., 2011). Not only does HC volume have predictive value in clinical status, but it is also closely linked to progression of clinical symptoms such as memory (Stoub, Rogalski, Leurgans, Bennett, & deToledo-Morrell, 2010). Hippocampal volume is a well-known and well-validated

risk factor for progression from MCI to AD, making it very logical to include in the diagnostic process (Li et al., 2016).

For many memory clinics that do use some sort of brain imaging in their diagnostic process, a radiology report is created from either visual inspection alone or with the aid of a VRS. VRS have demonstrated great value in clinics, but there is substantial evidence that volumetric analysis may be better than VRS. These scales can suffer interrater variability, which is normally eliminated by automated methods (G. B. Frisoni, Fox, Jack, Scheltens, & Thompson, 2010; Ph Scheltens et al., 1992). When comparing MCI patients to healthy controls, HC volume alone is better than a medial temporal lobe VRS (Varon et al., 2015). Both manual HC segmentation and multivariate analysis using automatic segmentation showed better accuracy than validated VRS tools (Westman, Cavallin, Muehlboeck, et al., 2011a).

There is substantial evidence for the use of MRI imaging, namely HC volume, in the diagnosis of AD (G. M. McKhann et al., 2011). However, nearly all of these studies use research based cohorts, and there are actually very few studies looking into the use of automated morphometry in a clinical setting. The general consensus is in order to be used as a diagnostic biomarker, a tool needs a sensitivity of at least 80% in both distinguishing AD from healthy controls and distinguishing AD from other dementias ("Consensus Report of the Working Group on," 1998; Hampel, Frank, et al., 2010; Hampel et al., 2012; Suppa et al., 2015). One of the few studies that did look at automated HC volume analysis in clinical populations found reasonable sensitivities, indicating there is potential for use as a clinical biomarker (Suppa et al., 2015).

6.1.3 Clinical Trial Objectives

This clinical trial aimed to evaluate the efficiency and usefulness of an automated brain morphometry tool, called ASSESSA®, as a clinical diagnostic aid for AD in a memory clinic setting. While this study assessed implementing automated brain morphometry in a clinical diagnostic routine, this was a pilot

project that aimed to gather initial information rather than a fully powered efficacy-type trial. The primary focus was to gain insight on the impact of this new technology on clinical practice. We aimed to ascertain if this technology was acceptable to clinicians in the memory services, in addition to the current traditional neuroradiology reports. The primary hypothesis was the additional automated morphometry report would give clinicians more confidence in their diagnosis, however we also aimed to see if a more specific diagnosis (such as AD versus unspecified dementia) was achieved.

6.2 METHODS

6.2.1 Ethics

Ethical approval of this study was granted by the National Health Service (NHS) Health Research Authority, London – City & East ethics committee (14/LO/0668). Copy of approval, and approval amendments, can be found in appendix 9.

6.2.2 Power Calculations for Sample Sizes

For the primary endpoint of change in diagnostic confidence a sample size of 80 (40 per arm) will be sufficient to achieve over 90% power to detect a clinically significant difference between groups (increase in confidence of at least 10% for the group with the morphometry report relative to the usual diagnosis control group, SD=15%) using a two-sided Student's independent t-test with equal group size and alpha = 0.05.

The estimates for effect size are derived from Grundman et al (Grundman et al., 2013). The diagnostic confidence in that study was increased by 21.6% (SD = 15.2) by adding a florbetapir scan to usual protocol. These calculations assume a more conservative, but still clinically significant estimate of 10% mean increase in diagnostic confidence, resulting in a sample size of 37 patients per arm for the desired power, or 74 patients in total for 90% power.

6.2.3 Participants

Similar to The BRCMEM Cohort, this pilot study used diagnostic-seeking patients from the South London and Maudsley NHS Trust (SLaM). These patients were referred to one of the memory services at the trust (Croydon Memory Service, Lewisham Memory Service, or Southwark and Lambeth Memory Service) by their general practitioner (GP) with suspicion of cognitive impairment.

6.2.3.1 Inclusion Criteria

The inclusion criteria are as follows: participants must have a working knowledge of English, the capacity to consent to both present and follow-up aspects of the study, no contraindications for an MRI scan, and an MMSE > 10 to rule out severe dementia. Patients must have been a minimum of 50 years old, to rule out early onset dementia due to genetic factors. Additionally, patients must be referred from one of the three aforementioned memory clinics.

A total of 98 participants were recruited for the study, however due to the inclusion criteria only 91 reached the randomisation stage of the study. Not participating in the study did not impact the patient's clinical care in any way.

6.2.4 Diagnostic Pathway

6.2.4.1 Initial Assessment and Recruitment

As per standard practice, if the GP referral has been accepted by the memory service, the patient and/or a carer was interviewed in an initial assessment. This initial interview is designed to measure cognitive and functional assessment, and is given by a doctor, nurse, psychologist, occupational therapist, or social worker trained in dementia diagnosis. The assessment includes cognitive concerns, mental state and symptoms, daily functioning and psychopathology, and personal, educational, family and medical history. Additionally, a variety of cognitive exams are administered, including: Addenbrooke's cognitive examination (ACE), the standardised mini-mental state examination (MMSE), Neuropsychiatric

Inventory (NPI), Bristol Activities of Daily Life Scale, the Geriatric Depression Scale (GDS), and Geriatric Anxiety Inventory.

After the initial assessment, the findings are discussed in a multidisciplinary team meeting the memory services regularly hold. This team is made up of senior medical professionals including the psychiatric consultants, as well as nurses, psychologists, occupational therapists and/or social workers. Here, the initial assessment results of patients are discussed, and it is determined whether cognitive impairment is present and further testing is needed. NICE guidelines recommend MRI scans in the investigation of cognitive impairment (National Collaborating Centre for Mental Health., 2007). In cases where there are contraindications for an MRI scan, such as metallic fragments in the eye or brain, magnetically activated pacemakers or other metallic pins or devices, or claustrophobia, a CT scan may be requested instead. Only patients who were then recommended for an MRI scan were sent the appropriate patient information sheet (PIS) for the current study.

Patients received the study's PIS at the same time as their MRI appointment time. The standard time between MRI referral and the scan is two weeks, giving all participants ample time to review the study and decide if they are interested in participating. Nearly all MRI scanning for SLaM memory services is done at the Centre for Neuroimaging Sciences (CNS), based at the Maudsley Hospital. When the patient arrived for the scan, they were prepared for their scan by the radiographers. After their scan was completed, they were approached by myself, the study coordinator. This brief meeting was to ensure interest in the study, assess capacity to consent to the study, and take informed consent if the patient was interested in participating. If consent was not obtained, for any reason including the patient was not interested in participating, no further action was taken and assessment and treatment proceeded as usual.

6.2.4.2 Scanning

The scanning procedure followed the standard memory clinic scans as described in the BRCMEM cohort chapter. This included the clinical high-resolution structural scan (T1 MPRAGE, ADNI sequence) previously described in *Chapter 2, Section 2.2.2 MRI Acquisition*. The scanning procedure was the same for all patients, regardless of which arm of the study they were randomised to.

6.2.4.3 Randomisation

Once the participant had consented to participation in the study, I confirmed the patient was eligible to participate and did not have an MMSE score < 10. Those with a MMSE less than 10 were dismissed from the study and those who were above were randomly assigned the participant to one of the study arms: intervention or control. Those in the control arm received treatment and diagnosis procedure as normal. Those in the intervention arm received the additional morphometry report.

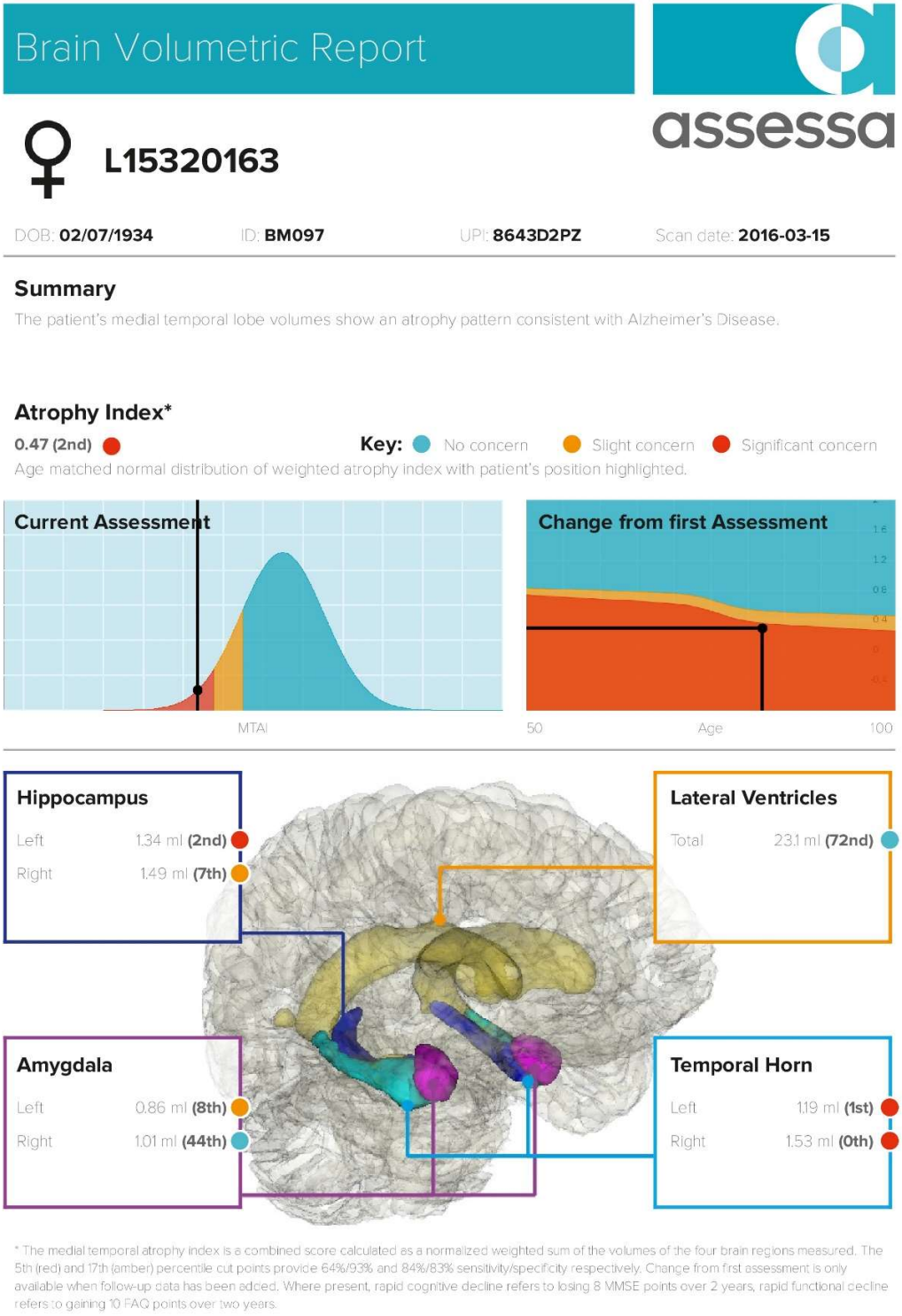
6.2.4.4 Radiological and Morphometric Assessment

After patients were scanned, MRI images were evaluated by a trained neuroradiologist. The neuroradiologist creates a report with qualitative assessment, concentrating on brain appearance and any abnormal findings suggestive of neurodegeneration. This radiological report is currently part of standard diagnostic practice, and all patients received one regardless of participation in the study or arm of the study they were assigned to. This report was then sent back to the referring clinicians to aid in diagnosis.

Patients that were assigned to the intervention arm received an additional morphometry report in addition to the neuroradiologist's qualitative assessment. These patients in the intervention arm had an anonymised copy of their MRI scan, stripped of any identifying data, transferred to IXICO (London, UK). IXICO is the scientific partner company specialising in the provision of biomarkers for clinical trials, with a special expertise in the morphometric analysis of brain images for potential quantitative markers of

neurodegeneration. IXICO produced a report with volumetric markers most relevant to dementia including hippocampal volume and other brain areas (Figure 6-2). In addition to the volumetric measurements, patients' values were compared against healthy age matched controls to see where patients fall on a normal distribution for people their age, which gives perspective to the volumetric measurement.

***Figure 6-2** - ASSESSA automated Morphometry Report*



6.2.4.5 IXICO Automated Brain Morphometry Report

IXICO's ASSESSA® is a CE marked medical device intended to assist clinicians in making a dementia diagnosis. ASSESSA® produces full volumetric reports on several brain structures subjected to atrophy and changes in dementia including the hippocampus, amygdala, temporal horn and lateral ventricles. These volumes are used to calculate a Medial Temporal Atrophy Index (MTAI) and are present with age-matched normal percentiles.

ASSESSA's® unique MTAI is calculated by using volumes attained from the Learning Embeddings for Atlas Propagation (LEAP) automated segmentation algorithm (Wolz et al., 2010). LEAP uses T1 MPRAGE to calculate volumes for the areas of interest. The MTAI is calculated as a weighted sum of volumes of both the left and right hippocampus, amygdala, temporal horns, and lateral ventricles. Volumes are normalised for head size using an affine scaling factor. Spaces segmented as cerebrospinal fluid (CSF) are weighted negatively whereas grey matter regions are weighted positively. Baseline lateral ventricle volumes are weighted at zero, and are only used in calculating longitudinal MTAIs, which were not used in the present study (Austin et al., 2014).

Age-matched normal percentiles were calculated by fitting a sigmoid model to the mean volumes of five year spans across a set of healthy people aged between 50 and 90 years old, from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset. This allows an age-matched normal distribution to be created for each individual subject's age.

The final report includes volumes for each of the listed brain structures, as well as a percentage of where the patient's volume falls on the normalise distribution. Additionally the MTAI is presented, with a lower number being indicative of more atrophy, alongside a percentile within a normal distribution of expected MTAIs. For all percentiles, colour coded cut-offs are provided for easier visualisation of where

a participant falls on the distribution, red for below 5th percentile and amber for below 17th percentile, while all other scores are coloured blue, indicating a normal percentile.

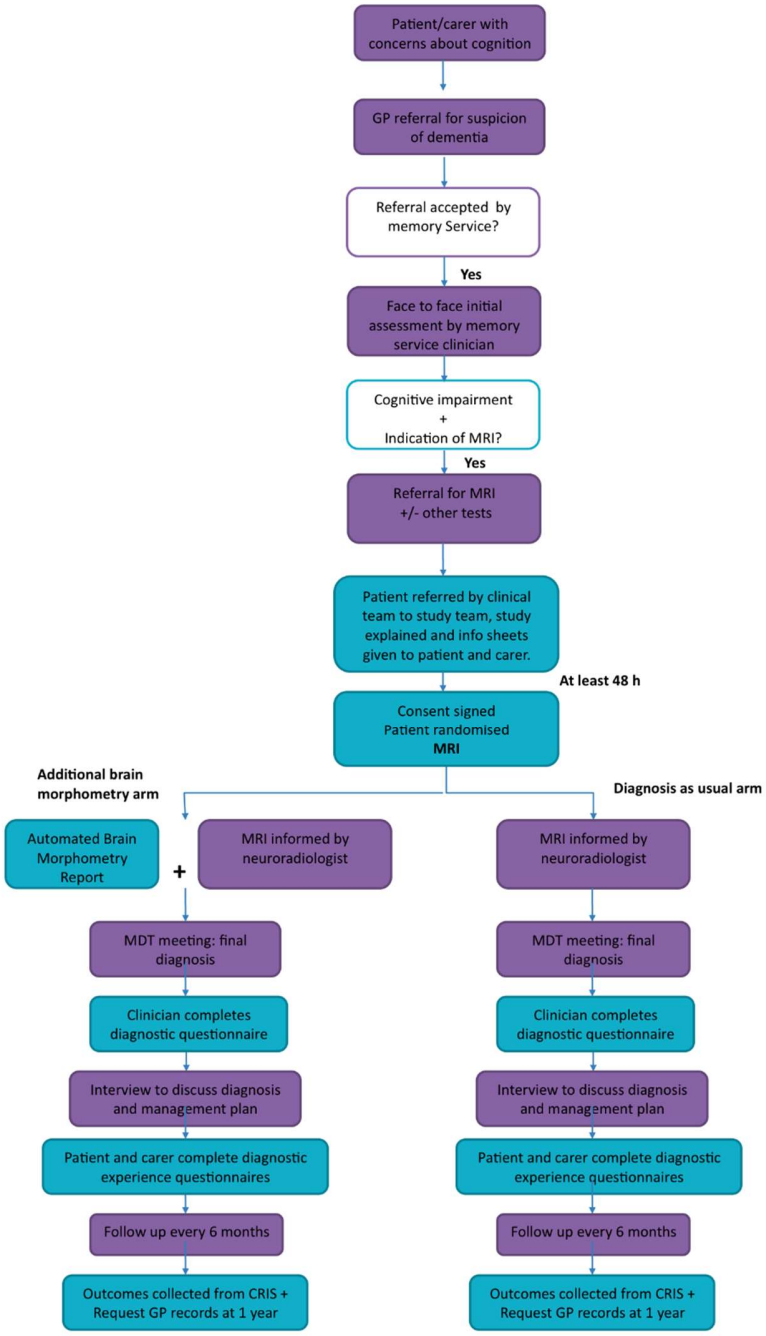
Patient's anonymised reports were then returned to me, and I linked the anonymised volumetric report to the individual patient and forwarded it on to the patient's referring clinician. Clinicians then used this report to aid in the diagnosis of the patient, in addition to the standard radiography assessment. Previous studies show these cut-off points provide 64%/93% and 84%/83% sensitivity/specificity respectively (Austin et al., 2014; IXICO plc, 2015).

6.2.4.6 Clinical Diagnosis and Outcomes

After all tests, including morphometry report if applicable, are received by the clinical team, the patient's care coordinator presents the results in the memory clinic's weekly multi-disciplinary team (MDT) meeting. This diagnosis may or may not be dementia, and may include a more specific etiological subtype such as AD, VaD, or MCI. Diagnosis and test results are then discussed with the patient and carers by the care coordinator in a face-to-face interview. In addition, a care plan is created that is most suited for the patient.

A flowchart of the clinical trial, including both control and intervention arms and overall diagnostic pathway, can be viewed in Figure 6-3.

Figure 6-3 – *Clinical Trial Flowchart. Purple boxes represent the normal diagnostic pathway, while blue boxes indicate clinical trial specific events.*



6.2.5 Clinician Survey

After every MDT meeting, a member of the clinical team was asked to fill out a survey about the diagnosis of each individual patient participating in the study. This survey was filled out regardless of whether the participant received the additional automated brain morphometry report.

This survey asks for an official diagnosis, on a scale from 1-5, how likely are the symptoms caused by either AD or VaD, and how confident the team is in their diagnosis. A full version of the survey can be viewed in Figure 6-4.

Figure 6-4 - Clinician Questionnaire, given to each clinician to fill out when diagnosing a patient at the MDT meeting.

South London and Maudsley NHS
NHS Foundation Trust

Study title: Automated brain morphometry for dementia diagnosis (BrainMeasure)

Clinician Questionnaire

We are asking you to complete this survey as a clinician for this patient, who is a participant in the BrainMeasure study.

Please complete the following questions on the basis of all the information on this patient (inclusive of the MRI neuroradiological report and, if available, the automated morphometry report).

Q1 On a score of 1 to 5 (where 1 is not at all likely and 5 is extremely likely), how likely is it that Alzheimer's disease is a cause for the patient's symptoms?

❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5

Q2 On a score of 1 to 5 (where 1 is not at all likely and 5 is extremely likely), how likely is it that cerebrovascular disease is a cause for the patient's symptoms?

❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5

Q3 What is the final diagnosis:

Q4 On a score of 1 to 5 (where 1 is not at all confident and 5 is extremely confident), how confident are you in the final diagnosis?

❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5

Please add here any additional comments:

About you:
Name:
Designation:
Memory Service:
Date:

Thank you for providing this information.

6.2.6 Statistical Analysis

All statistical analyses were performed with SPSS 24 software package, and considered significant at the $P < 0.05$ level. Any X^2 tests performed on a two x two table used continuity correction to measure significance.

6.2.6.1 Demographics

One way analysis of variance (ANOVA) was used to measure differences in age or MMSE score between the two conditions. A X^2 tests was used to measure differences in gender distribution between the two groups. For further analysis, we broke down diagnosis into seven categories: AD, Mild Cognitive Impairment (MCI), Mixed Dementia (MD), Frontotemporal Lobe Dementia (FTD), VaD, no diagnosis, or other (mainly included depression and anxiety). All 91 participants received a diagnosis that fell into only one of these seven categories.

6.2.6.2 Clinician Confidence in Diagnoses

Primary analysis looked at clinician confidence for the diagnosis given to each patient as reported in clinician survey. Unpaired t-test was used to compare each group, patients with and without additional brain morphometry report.

Finally, to ensure there were no biases, we compared mean clinician confidence for those surveys filled out by consultants versus another medical professional in the team, for each condition. Once again, unpaired t-tests were used.

6.2.6.2.1 Clinician Confidence within diagnostic groups

Using the separated diagnosis categories, clinician confidence in diagnosis was also compared between control and intervention arms using unpaired t-tests. The clinical trial was not originally powered for this kind of analysis, and these post-hoc tests are purely for exploratory purposes.

6.2.6.3 Clinician Rating of Likelihood of Vascular Dementia or Alzheimer's Disease.

For each patient, clinicians were asked on a scale of one to five how likely the patient's symptoms were to be caused by VaD or AD (1 being not likely at all, and 5 being extremely likely). Unpaired t-tests were used to compare the ratings for each group, as it has been used previously to measure increase in clinician confidence (Grundman et al., 2013). However, it should be noted that non-parametric testing, such as Wilcoxon or sign test, may also be appropriate given the ordinal nature of the data.

Pearson X^2 test was then used to determine the relationship between condition and diagnosis of VaD and AD, to test if one group was more likely to receive one of these diagnoses than the other. Participants were categorised as either receiving a diagnosis of AD and VaD or something else.

6.2.6.3.1 Clinician Rating of Likelihood of Vascular Dementia or Alzheimer's Disease within diagnostic groups.

Average rating of likelihood that AD or VaD caused a patient's symptoms was calculated for each diagnosis category. Differences between average in disease category was measured by one-way analysis of variance (ANOVA), excluding the FTD group as there was only one participant. Bonferroni post-hoc tests were used to measure which groups differed.

Each disease category was then analysed individually, to examine differences in clinicians' rating of likelihood a patient's symptoms were caused by AD or VaD differed between the intervention and control arms, using unpaired t-tests.

6.2.6.4 Number of Specific Diagnoses

We believed brain morphometry would result in more specific diagnoses for patients, meaning diagnoses with etiological qualifiers such as AD or VaD as opposed to unspecified dementia. For this

purpose, we broke down diagnosis into seven categories: AD, MCI, MD, FTD, VaD, no diagnosis, or other (mainly included depression and anxiety). All 91 participants received a diagnosis that fell into only one of these seven categories.

Pearson X^2 test was then used to test the relationship between condition and specificity of the resulting diagnosis. For this analysis, we separated participants into one of two groups specific or non-specific diagnosis. The non-specific group comprised of patients who received 'no diagnosis'. All other diagnoses, including non-dementia related ones such as depression and anxiety, were considered specific.

6.2.6.4.1 Number of more Specific Dementia Diagnoses

A subset of participants who ultimately received a dementia diagnosis (either AD, VaD, MD, FTD, or MCI; n=67) were also examined separately. Participants were categorised as either having a specific dementia diagnosis (AD, VaD, MD, or FTD) or a diagnosis of MCI. Pearson X^2 test was used to measure if condition significantly impacted specificity of dementia diagnosis.

6.3 RESULTS

6.3.1 Demographics

All sample characteristics are listed in Table 6-1. There were no significant differences between age, gender, or MMSE score between the two conditions. Table 6-2 lists the diagnostic breakdown of the two groups (Figure 6-5).

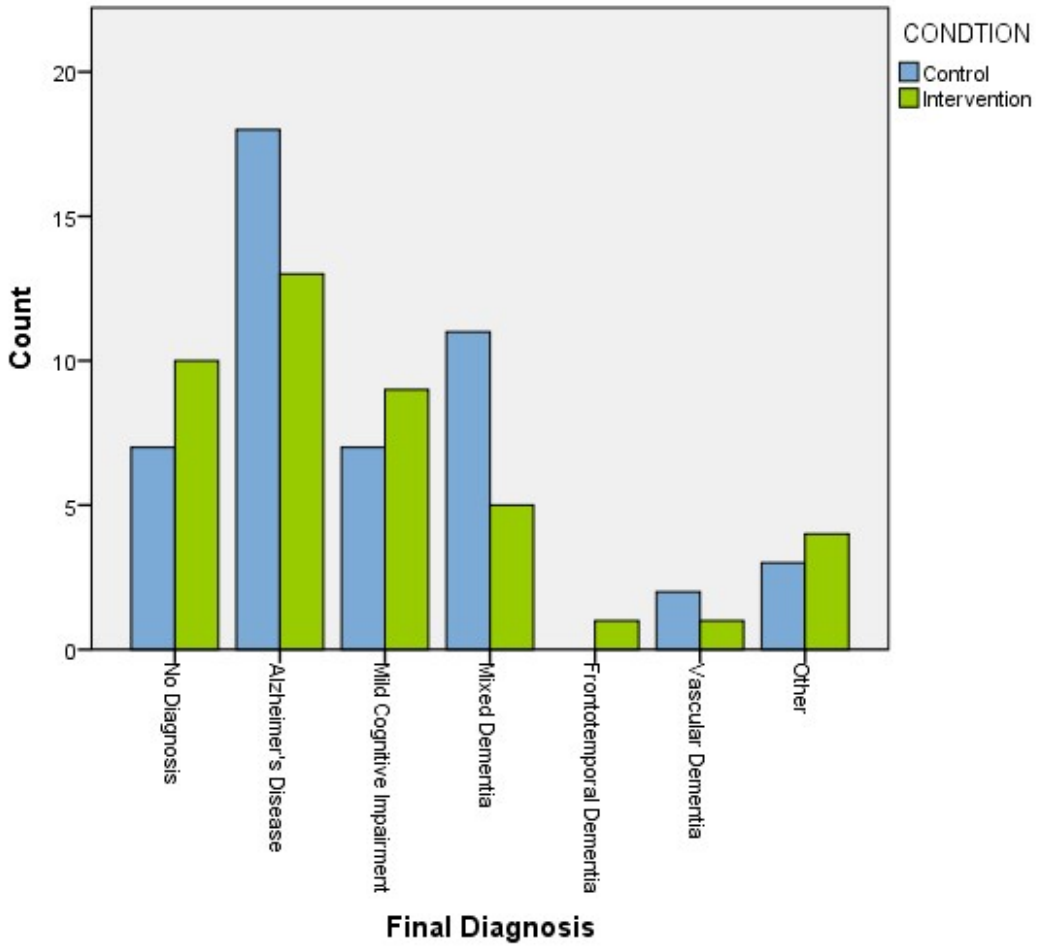
Table 6-1 – *Demographics of the Clinical Trial cohort, divided into control arm and intervention arm. Age and MMSE score = Mean (Standard Deviation). Significance for Age and MMSE score as measured by ANOVA; significance in Gender distribution as measured by X^2 tests. Only 36 in the control arm / 34 in the intervention arm had MMSE scores.*

	Control	Intervention	P-Value
Number	48	43	
Age	75.58 (8.6)	74.16 (10.6)	0.483
Gender (M/F)	19/29	21/22	0.788
MMSE Score	24.33 (4.62)	24.74 (3.89)	0.696

Table 6-2*- Diagnosis breakdown of the cohort, divided into control arm and intervention arm.*

	Control	Intervention	Total
No Diagnosis	7	10	17
Alzheimer's Disease	18	13	31
Mild Cognitive Impairment	7	9	16
Mixed Dementia	11	5	16
Frontotemporal Dementia	0	1	1
Vascular Dementia	2	1	3
Other	3	4	7
Total	48	43	91

Figure 6-5 – *Graphical representation of Diagnostic breakdown between the two groups.*



6.3.2 Clinician Surveys

6.3.2.1 Clinician Confidence

6.3.2.1.1 Confidence Rating

While clinicians appear to be slightly more confident with the automated volumetry reports (control=3.63 vs intervention=3.91) the difference was not significant (p=.278) (Table 6-3).

There were also no significant differences in clinician confidence depending on whether or not the consultant old age psychiatrist filled out the survey, or another member of the MDT team (consultant=3.73 vs non-consultant=3.92; p=.577).

Table 6-3 – *Clinician Survey Results. All represent the mean response (on a scale of 1-5; whereas 1 is not at all and 5 is extremely) and (standard deviation). * denotes significance at p < 0.05 level.*

	Control	Intervention	P-Value
How likely is this AD?	3.02 (1.26)	2.91 (1.39)	0.684
How likely is this VaD?	2.35 (1.21)	1.83 (1.05)	0.029*
How confident in final Diagnosis?	3.63 (1.23)	3.91 (1.24)	0.278

6.3.2.1.2 Clinician Confidence Rating Within Diagnostic Groups

When looking at clinician confidence in specific diagnostic categories, differences emerged which did not exist when analysing the sample as a whole. In patients that ultimately received a diagnosis of AD, clinicians were significantly more confident in their diagnosis with the addition of the automated morphometry report (intervention group) (control=3.83 vs intervention=4.53; p=0.026) (Table 6-4). Additionally, clinicians were more confident with the automated morphometry report in cases that were diagnosed with something other than dementia, such as depression or anxiety (control=2.00 vs intervention=4.50; p=0.022) (Table 6-4). Confidence did not differ in other diagnostic categories, and a full list of results is listed in Table 6-4.

Table 6-4 – *Clinician Confidence in diagnosis, broken down by ultimate diagnosis. All represent the mean response (on a scale of 1-5; whereas 1 is not at all and 5 is extremely) and (standard deviation). * denotes significance at p < 0.05 level.*

	Control		Intervention		P-Value
	N	*Average*	*N*	*Average*	
No Diagnosis	7	2.14 (1.57)	10	2.80 (1.81)	0.451
Alzheimer's Disease	18	3.83 (0.99)	13	4.53 (0.52)	0.026*
Mild Cognitive Impairment	7	3.86 (0.69)	9	3.78 (0.83)	0.842
Mixed Dementia	11	4.36 (0.50)	5	4.00 (0.71)	0.256
Frontotemporal Dementia	0	-	1	5.00	-
Vascular Dementia	2	4.50 (0.71)	1	4.00	0.667
Other	3	2.00 (1.00)	4	4.50 (1.00)	0.022*

6.3.2.1.3 Clinician Survey – Qualitative Evidence

While the scaled survey format is useful, there are more subtleties with each diagnosis that cannot be determined from a simple numerical score. The commentary clinicians gave on the surveys was perhaps even more telling than the confidence score.

For specific cases, it was very clear that the morphometry report was indeed helpful, and pushed them to conclude a diagnosis:

"Useful to have the volumetry in this case to firm up the diagnosis"

"The morphometry confirmed [the neuroradiologist's] report of vascular changes and no hippocampal problems – initial thoughts were this was likely to be more mixed."

"More confident with the normal hippocampi – looked like vascular MCI clinically …"

"Helped as everything static except subjective complaint and the normal hippocampi strengthen diagnosis"

"Morphometry shows OK hippocampal volumes – history very characteristic and some white matter change on MRI so went with a mixed type"

And it is clear for certain cases in the control group, the volumetry report was needed:

"Borderline cognitive issues and nothing much on scan… still awaiting neuropsych. This is one where the morphometry would have been of help."

"This is one where the morphometry report might have been able to bring a bit more clarity. Fairly normal scan – history classic AD – some vascular risk"

Additionally, it seems though the morphometry report helped rule out an AD diagnosis in some cases. While this may not be reflected in clinician confidence, or result in more specific diagnoses for the intervention group, it is still paramount in making sure patients receive the correct diagnosis.

"The volumetry helped reduce the likelihood that this is AD"

"Diagnosis not clear – awaiting neuropsych. The morphometry does back up the scan report that [it's] probably not AD, so that helps but one remains unsure .."

Conversely, there were some patients assigned to the intervention group that seemed to not need the morphometry report:

"History highly suggestive, report from radiologist says it too. Little to be gained from morphometry"

"History + original MRI report enough to make confident"

6.3.2.2 Clinician Rating of Likelihood of Vascular Dementia or Alzheimer's Disease.

When asked what is the likelihood that VaD caused the patient's symptom, clinicians were significantly less likely to attribute the patients' symptoms to VaD in the intervention group (control=2.35 vs intervention=1.83; p=.029) (Table 6-3).

This difference was not found in the likelihood that AD caused the patient's symptoms (control=3.02 vs intervention=2.91; p=.684) (Table 6-3).

Table 6-3 – *Clinician Survey Results. All represent the mean response (on a scale of 1-5; whereas 1 is not at all and 5 is extremely) and (standard deviation). * denotes significance at p < 0.05 level.*

	Control	Intervention	P-Value
How likely is this AD?	3.02 (1.26)	2.91 (1.39)	0.684
How likely is this VaD?	2.35 (1.21)	1.83 (1.05)	0.029*
How confident in final Diagnosis?	3.63 (1.23)	3.91 (1.24)	0.278

There were no significant differences between the likelihood to receive a diagnosis of AD or VaD versus another diagnosis, including another form of dementia, a psychiatric disorder, or no diagnosis, for either group (Table 6-5).

Table 6-5 – *Distribution of patient diagnosis between the two conditions, as measured by* $X^2 = .497$.

	Control	Intervention	Total
VaD or AD Diagnosis	20	14	*34*
Other Diagnosis	28	29	*57*
Totals	*48*	*43*	*91*

6.3.2.2.1 Clinician Rating of Likelihood of Vascular Dementia or Alzheimer's Disease within diagnostic groups.

Average rating of likelihood that AD or VaD caused a patient's symptoms was calculated for each diagnosis category (Table 6-6). As expected, there were significant differences between group averages, and the complete ANOVA with Bonferroni post-hoc tests can be found in appendix 10.

Table 6-6 – *Average clinician rating of likelihood that AD or VaD caused a patient's symptoms.*

	N	How likely AD	How likely VaD
No Diagnosis	17	1.94 (0.97)	1.88 (0.86)
Alzheimer's Disease	31	3.97 (0.98)	1.65 (0.88)
Mild Cognitive Impairment	16	2.00 (0.63)	2.06 (1.18)
Mixed Dementia	16	3.81 (0.83)	3.22 (1.11)
Frontotemporal Dementia	1	3.00 (0.00)	3.00 (0.00)
Vascular Dementia	3	2.33 (1.16)	4.00 (1.00)
Other	7	1.57 (0.79)	1.29 (0.49)

When examining those who received a final diagnosis of AD, clinicians were more likely to attribute a patient's symptoms to AD with the addition of the automated morphometry report (control=3.67 vs intervention=4.39; p=0.026). No other diagnostic category showed this difference (Table 6-7)

Table 6-7 – *Clinician likelihood to attribute a patient's symptoms to AD (how likely is this AD?), broken down by ultimate diagnosis. All represent the mean response (on a scale of 1-5; whereas 1 is not at all and 5 is extremely) and (standard deviation). * denotes significance at p < 0.05 level.*

	Control		Intervention		P-Value
	N	*Average*	*N*	*Average*	
No Diagnosis	7	2.43 (1.13)	10	1.60 (0.70)	0.081
Alzheimer's Disease	18	3.67 (1.14)	13	4.39 (0.51)	0.026*
Mild Cognitive Impairment	7	1.86 (0.69)	9	2.11 (0.60)	0.445
Mixed Dementia	11	3.64 (0.92)	5	4.20 (0.45)	0.222
Frontotemporal Dementia	0	-	1	3.00	-
Vascular Dementia	2	2.00 (1.41)	1	3.00	0.333
Other	3	1.67 (0.58)	4	1.50 (1.00)	0.809

Conversely, when looking at the same group of patients that received a diagnosis of AD, clinicians were less likely to contribute symptoms to VaD with the added morphometry report (control=1.89 vs intervention=1.31; p=0.045). Again, no other diagnostic category showed this difference (Table 6-8).

Table 6-8 – *Clinician likelihood to contribute a patient's symptoms to VaD (how likely is this VaD?), broken down by ultimate diagnosis. All represent the mean response (on a scale of 1-5; whereas 1 is not at all and 5 is extremely) and (standard deviation). * denotes significance at p < 0.05 level.*

	Control		Intervention		P-Value
	N	*Average*	*N*	*Average*	
No Diagnosis	7	2.14 (0.90)	10	1.70 (0.82)	0.310
Alzheimer's Disease	18	1.89 (1.02)	13	1.31 (0.48)	0.045*
Mild Cognitive Impairment	7	2.29 (1.25)	9	1.89 (1.17)	0.524
Mixed Dementia	11	3.09 (1.22)	5	3.50 (0.87)	0.513
Frontotemporal Dementia	0	-	1	3.00	-
Vascular Dementia	2	4.50 (0.71)	1	3.00	0.667
Other	3	1.67 (0.58)	4	1.00 (0.00)	0.184

6.3.3 Number of Specific Diagnoses

6.3.3.1 All Diagnoses

The majority of patients did receive a diagnosis, although not all were dementia related. In total, 74 of the 91 people were grouped as having a specific diagnosis. Chi-squared tests revealed specific diagnoses showed no evidence of a difference between the conditions (p=.429) (Table 6-9).

Table 6-9 *– Group distribution of specific diagnoses, as measured by* $X^2 = .429$.

	Control	Intervention	Total
Specific Diagnosis	41	33	*74*
No Diagnosis	7	10	*17*
Totals	*48*	*43*	*91*

6.3.3.2 Dementia Diagnoses

When only looking at the subset of patients whom received a dementia diagnoses (n=67), there were no significant differences between receiving a diagnosis of specific dementia (AD, MD, VaD, or FTD) versus MCI (p=.362) between the control and intervention condition (Table 6-10).

Table 6-10*- Group distribution of specific dementia diagnoses versus MCI, as measured by* $X^2 = .362$

	Control	Intervention	Total
Specific Dementia Diagnosis	31	20	*51*
MCI	7	9	*16*
Totals	*38*	*29*	*67*

6.4 DISCUSSION

Hippocampal volumetry use for dementia diagnosis has been gaining acceptance in recent years, and several studies have looked at the benefits of volumetric use versus standard neuroradiological reporting (Klöppel et al., 2008; Ross, Ochs, Seabaugh, Shrader, & Alzheimer's Disease Neuroimaging

Initiative, 2013; Westman, Cavallin, Muehlboeck, et al., 2011a). Ross and colleagues found that automated methods were more sensitive at finding atrophy than neuroradiologists, however this was not in dementia cases (Ross et al., 2013). Multivariate image analyses, and even using hippocampal volume alone, have also been shown to be more sensitive at detecting dementia than neuroradiologists using a structured visual rating scale (Klöppel et al., 2008; Westman, Cavallin, Muehlboeck, et al., 2011a).

There are several approved tools for automated volumetry measurement in clinics, including ASSESSA® based on LEAP, and Neuroquant based on FREESURFER (Brewer, Magda, Airriess, & Smith, 2009). While they are based on different segmentation algorithms, their performance is similar (Yu et al., 2014). These methods are considered good, and useful to have when reviewing a patient's case, but are not sufficient for a dementia diagnosis alone (Engedal, Brækhus, Andreassen, & Nakstad, 2012).

6.4.1 Quantitative and Qualitative Survey Results

6.4.1.1 Clinician Confidence in Diagnosis

While statistical analyses showed there were no significant differences in clinician confidence overall, there was a plethora of qualitative evidence suggesting that this is still a potentially useful tool in a memory clinic setting. A few common themes can be found when reviewing the clinicians' comments on the diagnostic process. It seems that often the report was very helpful, and pushed towards a specific diagnosis, or would have been helpful to have. For others, while it did not help result in a specific diagnosis, it was useful in ruling out AD. In addition, there were a number of patients that the clinicians felt did not need the morphometry report. These themes taken together suggest that it may be that a subset of patients benefit from such automated morphometry reports more than others.

When looking at specific diagnostic categories, a significant difference was found in clinician confidence for those with AD or some other form of diagnosis. It is logical these two groups would benefit most

from the additional automated morphometry report, as hippocampal volume is directly related to AD. For those diagnosed with a non-dementia condition such anxiety or depression, the automated morphometry report may have assured clinicians they can rule out a diagnosis of AD or dementia. Both groups are likely to exhibit one of the extremes, either very little or significant atrophy, on the automated morphometry report. This added confidence may not be seen in other categories, as the automated morphometry report does not add new information related to these conditions, or because the automated morphometry report did not show pronounced (or little) atrophy in these subjects.

It is always challenging implementing a new tool into routine healthcare streams, especially with concerns over cost, and both time and resources used for implementation. There is a clear set of benefits to some patients, namely those who do have AD, but it may not be necessary for everyone who finds themselves in a memory clinic. It is well documented that AD has a long prodromal stage, where brain changes are beginning to occur with minimal symptoms, that may be confused for another type of disorder (Sperling et al., 2011). Unlike most well-defined research cohorts, clinical cohorts can include people anywhere along this trajectory. Subjects who have yet to have produced atrophy, but have slight atrophy which may or may not be indicative of AD, may need a diagnosis based on other factors such as white matter changes as described on the neuroradiological report.

For those who are further on the AD progression timeline, it makes sense that atrophy is easily visualised with the naked eye, and in combination with severe clinical symptoms there is little need for extra support, such as an automated volumetry report. According to NICE guidelines, MRI imaging may not be necessary for those presenting with moderate to severe dementia, if the diagnosis is already clear, suggesting the patients with the most pronounced atrophy may not have been scanned in the first place (National Collaborating Centre for Mental Health., 2007). The increase in confidence in AD patients may be due to the inability to discern the extent of the atrophy with an unstructured report, as compared to a volumetric measurement and a score that describes the percentile the patient fits

compared to healthy age matched controls. The automated volumetry reports potentially hold great promise in helping clinicians discern cases that are less clear cut, with atrophy present and mild subjective memory complaints, which most likely describe the patients in this cohort that ultimately received an AD diagnosis.

Furthermore, the SLaM memory services in this study have access to tertiary level neuroradiologists with special expertise in dementia imaging. This level of expertise in assessing brain scans is not generally available to memory services, and may have reduced the added usefulness of morphometry. It may be that this sort of tool will have a more pronounced effect in memory clinics and primary care centres which do not have access to such a high level of expertise.

6.4.1.2 Clinician Rating of Likelihood of Vascular Dementia or Alzheimer's Disease.

The clinicians were significantly more likely to conclude VaD may have contributed to a patient's symptoms in the control group than the intervention group, and this difference remained in the AD patients when looking at each diagnostic group separately.

While this report only contained volumetric information on very specific brain regions and no information on white matter, seeing a distinguished pattern of atrophy centralised in the medial temporal lobe may have helped rule out VaD for a number of patients. VaD does not have the same neuropathological pattern that centralises around the hippocampus and medial temporal lobe that is seen in AD (O'Brien & Thomas, 2015b). Hippocampal atrophy is not as prevalent or severe in VaD, and while patients with VaD have smaller hippocampi than healthy controls, they still have larger hippocampi than those diagnosed with AD (Kim et al., 2015). Additionally, cognition in VaD does not always correlate with hippocampal volume (Mungas et al., 2002).

There was no difference in clinicians' likelihood to conclude that AD was the cause of a patient's symptoms between the two groups, when looking at the entire cohort. For AD patients specifically,

clinicians were significantly more likely to attribute a patient's symptoms to AD in the intervention group. This may also be attributed to AD patients having the most pronounced hippocampal atrophy on the reports.

While patients in the control group were more likely to have clinicians believe VaD was a cause of their symptoms, neither group was more like to receive a diagnosis of VaD or AD than other condition.

6.4.1.3 Number of Specific Diagnoses

Contrary to our original hypothesis, having the automated morphometry report did not result in clinicians giving a more specific diagnosis. Unexpectedly, none of the 91 participants received a diagnosis of unspecified dementia, which is not the case in the earlier described BRC memory clinic cohort (*Chapter 2: The BRC Memory Clinic Cohort*) and other memory clinics (Falahati et al., 2015). We believed that the control group would receive more of this type of diagnosis, however this finding suggests that this may not be as common as a diagnosis as previously thought. We are unsure if these patients are more likely to receive no diagnosis, or be categorised into a specific type of dementia that is suspected, or categorised as MCI as it is often used as a precursor to AD, MD, or even VaD.

Qualitative evidence from the clinicians' comments revealed that the automated morphometry report was helpful in ruling out dementia. While this may result in no diagnosis, it may also be instrumental in preventing a wrong diagnosis. Wrong diagnoses are just as harmful as missed and delayed diagnosis, and can not only result in lost opportunities for correct treatment and therapies, but can also drain resources when they may not be needed or useful (Bradford et al., 2009). Moving forward, it would be interesting to follow this cohort and look at any changes made in diagnoses, and see whether those receiving the morphometry report were more likely to keep their original diagnosis. Because misdiagnosis is such a big concern in making diagnoses timelier, this tool can be useful in achieving earlier diagnoses in dementia (Dubois, Padovani, et al., 2016; Gaugler et al., 2013).

A secondary analysis on the subset of patients who received a dementia diagnosis examined whether patients in one group or the other were more likely to receive a diagnosis of MCI or some other form of dementia (AD, VaD, MD, or FTD). While MCI may be considered a substantial diagnosis on its own, it could also be categorised as a non-specific diagnosis. Amnesic MCI is often considered a precursor to AD, however there are different forms of the disorder (such as MCI due to vascular impairment) that were not distinguished in these diagnoses. Additionally, patients diagnosed with MCI may not go on to develop AD, and either remain with MCI or revert to normal cognition. A majority (60-70%) of cases of amnestic MCI can be attributed to AD pathology mixed with another type of dementia pathophysiology such as white matter changes and cerebrovascular disease, or Lewy body disease (Jicha et al., 2006; Ronald C. Petersen et al., 2006). This reinforces that while MCI may often be a precursor to AD, it is a very heterogeneous condition and may be a precursor to another type of dementia or a stand-alone condition (Gordon & Martin, 2013; Janoutová, Šerý, Hosák, & Janout, 2015).

6.4.2 Limitations

As with any study, there was numerous limitations that may have contributed to some of our findings. Firstly, this was a pilot study and not a fully powered efficacy study. It is very possible that our sample sizes were simply not large enough, and more data is needed to truly see the useful effects of this tool in a memory clinic. There is evidence that significance thresholds may need to be reconsidered for pilot type studies, and this may need to be considered when interpreting results (Lee, Whitehead, Jacques, & Julious, 2014). Most of the group sizes once broken down by diagnosis were extremely small, and therefore were not sufficient to detect differences. Additionally, extremely small sample sizes may not actually be representative of a disease population. Because these extremely small sample sizes, used solely for exploratory analysis, no corrections were made for multiple comparisons, and significance between disorders may not be present if a corrected p-value was used.

For the analyses of clinical confidence, and likelihood of AD or VaD, unpaired t-tests were used to measure mean differences between the two groups. While this statistical test was used previously in measuring increase in clinician confidence, it may not be the most appropriate for the given dataset (Grundman et al., 2013). There was no assessment of the normality of the distribution of the data, and therefore non-parametric tests may be more appropriate. Non-parametric tests use ranked order of observations, instead of the measurements themselves, to distinguish group differences. In addition to skewed data, it can also be useful for tests that have a small range of possible values, such as the 1-5 scale used in the survey. These tests have almost as much statistical power as t-tests when the samples are large, however they do not provide estimates of means or confidence intervals (Douglas G. Altman & Bland, 2009). It should be noted that different statistical analyses can reveal different results, and this should be remembered when interpreting the results.

With any new tool, there comes complications with implementation. While clinicians are most likely very familiar with the concept of hippocampal atrophy in AD and dementia, a volumetry report that clinicians are unfamiliar with may take time before its full potential is realised. Clinicians are very busy, and often working with limited resources, which may cause a delay in filling out final clinician surveys. While the surveys are intended to be filled out jointly with the entire MDT team, some may have been filled out after the diagnosis was made. Clinicians are always able to look at case notes, but it is unclear what kind of impact a delay in survey completion could have on the results. Lastly, because results are based solely on clinician self-reports, it is important to consider the possible interpretations of the question *'How confident are you in this diagnosis?'*. Because there were multiple clinicians filling out these surveys, there may be a difference in what each clinician considers confident. Some may be likely to say they are confident in no diagnosis, while some may believe they cannot be confident in no diagnosis. The qualitative evidence certainly helps discern clinicians' feelings, but more work could be done to more closely dissect their scores.

When making diagnoses, clinicians may take into consideration inherent differences in ethnic populations. It is well documented that various populations are affected differently by various types of dementia (Anderson, Bulatao, Cohen, & National Research Council (US) Panel on Race, 2004). It may be that, unintentionally, clinicians are more likely to diagnose based on a patient's ethnicity based on previous literature. Additionally, comorbidities are taken into consideration when assessing patients. These two types of information were not looked at in the present study, and may have had interesting effects on clinician confidence and type of diagnosis.

6.4.3 Future Work

While the qualitative evidence from the clinicians' comments is encouraging, more studies need to be done to measure the efficacy of this as a diagnostic tool in memory clinics. It can be especially hard to test the diagnostic accuracy of a new test when the reference test, which is usually a clinical diagnosis, is an imperfect test itself (Coart et al., 2015). Officially, the gold standard of dementia diagnosis is a postmortem examination revealing relevant AD pathology, however there are many issues with using this as a reference test (Philip Scheltens & Rockwood, 2011). Firstly, lab results can differ with their postmortem examination results, especially given the heterogeneity of neuropathology of AD and lack of standardisation. It can also be problematic in early stages of the disease, when the diagnosis is not clear, such as mild AD or MCI. Ultimately, there lacks a definitive relationship between the neuropathology and clinical stages of AD, especially in the oldest where the disease is most common, which makes postmortem an insufficient reference point (Savva et al., 2009; Philip Scheltens & Rockwood, 2011). While biomarkers are a popular option for replacement, they can also be fallible and lack lab measurement standardization (Coart et al., 2015; Philip Scheltens & Rockwood, 2011).

It may be necessary to move toward integrating multiple sources of information, from a variety of biomarkers and clinical assessments, for reference tests given the complexity of the disease and lack of gold standard (Coart et al., 2015; Philip Scheltens & Rockwood, 2011). The heterogeneity of AD, and

variety of neuropathological presentations must be taken into consideration when examining a tool's validity, as there must be an extension of what includes a 'normal' presentation of AD (Philip Scheltens & Rockwood, 2011). One groups use of a bayesian model to integrate various sources of diagnostic information, including clinician diagnosis and CSF biomarkers, four it can account for the imperfection in tests by combining more data sources (Coart et al., 2015). These studies show the importance of considering multiple biomarkers when judging diagnostic accuracy of a new tool, and should be looked at in the future when assessing this automated morphometry report.

6.4.3.1 Future work within this pilot

There are several secondary hypotheses that may be examined in the future. The ultimate aim of using this tool is two-fold, to increase clinician's confidence in their diagnosis, and in turn to allow clinicians to make a more confident diagnosis earlier on. As discussed earlier, a more timely diagnosis allows people better access to care, a more positive experience, and can even potentially have economically impact on health care systems (Dubois, Padovani, et al., 2016). One potential analysis could examine time from referral to diagnosis, and whether those with the additional volumetry report were diagnosed more quickly. Using the electronic health records available through SLaM, we could access both date of referral and date of diagnosis, and measure group differences in average time to diagnosis using independent sample t-tests. Some of the other differences we believe would be directly impacted by this earlier diagnosis would be less utilisation of extra resources like additional visits, retesting, and use of other scanning modalities such as positron emission tomography (PET). Additionally, we would expect those in the intervention condition who are diagnosed with AD would then receive an earlier prescription of cholinesterase inhibitors such as donepezil, rivastigmine, or galantamine, due to their earlier diagnosis. It would also be interesting to look at any changes in diagnoses made in follow-up appointments, to see if the volumetry reports may have lead clinicians to a correct diagnosis earlier. Finally, we would expect that overall patient and carer experience would be more positive, a common

finding with earlier diagnoses (Boise et al., 1999; de Vugt & Verhey, 2013). This would be measured with follow-up surveys sent to patients one year from their MRI scan.

Lastly, within this study it would be interesting to measure differences in diagnoses based on ethnicities and comorbidities. As previously mentioned, it is well documented that dementia type proportions vary within different populations, and it would be interesting to see if this trend also held true in the current study. It would also be interesting to see if different diagnoses were more or less likely based on various comorbidities, to test whether or not clinicians are more likely to diagnose patients with vascular risk factors, such as high-blood pressure and type II diabetes, with VaD. Ethnic information and medical history are also available on the hospitals electronic patient record system, and would be easily accessible.

6.4.3.2 Potential Uses for an Automated Morphometry Reporting System

Even though more work needs to be done to validate this as a tool to be used in clinical practice, there are is a large variety of applications that could follow.

6.4.3.2.1 Potential Uses in Memory Clinics and Primary Care

While the current diagnostic standards are based on clinical symptoms alone, it is a logical next step to begin including brain imaging (G. M. McKhann et al., 2011). The ASSESSA® automated morphometry report also supports a longitudinal feature, and can create an MTAI using longitudinal information from multiple scans and cognitive exams. There is evidence that rate of atrophy can predict clinical status better than a single volumetric measurement alone (C. R. Jack et al., 2005). Following our cohort of patients, and giving them subsequent volumetry reports at each follow up visit may have an even greater impact. Using more scanning information, such as white matter lesion load, may also give greater insight into dementia type. While this tool may be useful, it would only be useful if implemented

correctly. As previously mentioned, more clinics would need to provide MRI scans for all memory clinic patients.

It has been found that from initial symptom presentation, a dementia diagnosis usually takes between 18-30 months, but can take up to four years in primary care services (Bamford, Eccles, Steen, & Robinson, 2007). Primary care services are often already inundated, and since they are not specialist memory services dementia diagnoses are often missed. Previous efforts with educational interventions, such as practice based workshops and decision support systems, were not effective in increasing detection rates or speeding up time to diagnoses (Wilcock et al., 2013). An easy to use tool, such as ASSESSA®, with easily interpreted data and normalised scores may assist general practioners in identifying potential dementia cases. As previously discussed, clinician confidence may not have increased with the additional use of such a tool because of the high expertise of the neuroradiologists and consultants at the SLaM's memory services, and it may prove to be more effective at increasing diagnostic confidence in a primary care setting.

6.4.3.2.2 Potential Uses in Clinical Trials

In addition to the clinic, this too may prove to be useful in clinical trials and other forms of research. The volumetric measurements could provide quantitative data about rate of atrophy in drug trials, for more comprehensive interpretation of the efficacy of a given drug. It could also be used as a screening tool, to make sure those recruited into clinical trials actually do have AD or dementia, as a large percentage of drug trials fail because they may be targeting the wrong disease population (Mangialasche, Solomon, Winblad, Mecocci, & Kivipelto, 2010). Additionally, it is found hippocampal volumes can be useful in creating cut-offs in clinical trials, and determining patient groups (Yu et al., 2014).

6.5 CONCLUSION

Use of automated morphometry reports that included hippocampal, amgydalar, and ventricular volume in a memory clinic was examined. While the use of automated morphometry reports did not increase clinician confidence in diagnosis overall, exploratory post-hoc tests suggest it did improve confidence in patients that were ultimately diagnosed with AD. Qualitative evidence from the surveys show the clinicians find this tool useful in a subset of cases, and it may be beneficial for clinicians to have when making a diagnosis. While the automated morphometry reports did not result in more specific diagnoses, further investigation is needed to examine patient outcomes with and without the automated morphometry report.

7 GENERAL DISCUSSION

7.1 PURPOSE AND RATIONALE

The purpose of this PhD thesis is to explore the application of common used research techniques in Alzheimer's Disease (AD) and dementia studies in a clinical cohort. While recommended, imaging biomarkers are still not in the core diagnostic criteria of AD or Mild Cognitive Impairment (MCI) (Albert et al., 2011; G. M. McKhann et al., 2011). More validation of these biomarkers is needed, especially in clinical cohorts. While research cohorts like the Alzheimer's Disease Neuroimaging Initiative (ADNI) (R C. Petersen et al., 2010) and AddNeuroMed (Simmons et al., 2009) have been invaluable to AD research in the past decade, they are still research based cohorts and are therefore not always representative of the general population. A key factor in developing new biomarkers is ensuring their ability to apply to a majority of the population.

7.2 Review of Findings

This thesis focused on the use of research techniques in a clinical cohort, using EHRs. Table 1 shows a summary of findings in this thesis.

Table 7-1 – *Summary of findings from each study included in this thesis.*

Study Title	Summary of Findings
Correlation of MMSE score and Hippocampal Volume in a Memory Clinic Cohort	A large cohort of memory clinic patients' MRI scans were linked with their EHRs. This is the one of the first instances of MRI automated volumetric data and EHR linkages, and paves the way for future research. As expected, MMSE score was positively correlated with hippocampal volume, and this correlation was strongest in those with AD.
OPLS in a Memory Clinic Cohort	OPLS multivariate analysis has been examined in research cohorts numerous times, and have found to classify AD and healthy controls with relatively high accuracy. While the models did not perform as well in clinical cohorts, they still performed relatively well. This may be a useful clinical tool in the future, especially with the addition of other modalities such as CSF measures or cognitive test scores.
White Matter Hyperintensities and the Underdiagnosis of Mixed Dementia in a Memory Clinic Cohort	Using automated white matter hyperintensity and volumetric measures, groups were created to identify the distribution of AD, VaD, and MD pathology in memory clinic patients. Hard defined cut-off points may not be useful currently, but with further research and identification of other sub-group cut-offs (such as MCI) they could be useful. Additionally, there is substantial evidence that MD may be underdiagnosed in a memory clinic setting.
BrainMeasure: Automated Morphometry for Dementia Diagnosis	Use of automated morphometry reports (including hippocampal, amygdalar, and ventricular volumes) was examined in a clinical trial. The use of automated morphometry reports did not increase clinician confidence in diagnosis overall, however exploratory post-hoc analyses suggest it may improve confidence in those ultimately diagnosed with AD. Qualitative evidence from surveys show clinicians find the tool useful, especially for a subset of unclear cases. Further investigation is needed to examine the use of this tool in a clinical setting.

7.3 Implementation of Research Techniques in Clinical Cohorts

While ADNI and AddNeuroMed have made a tremendous impact on a variety of research areas, such as basic research, clinical trials, and data sharing, these cohorts still have their limitations. Within a decade, well over 600 publications have been generated with the ADNI dataset (Weiner et al., 2015). The ADNI cohort is mostly made of an amnestic clinical population, and is not selected based on the actual

population. These subjects have limited comorbidities, and many with pre-existing conditions are excluded from study participation. Because of this, the findings from these studies cannot always be directly extrapolated to the general population. One of the advantages of a clinical cohort is it mitigates this confound, and it is important to continue this with other research tools to ensure their usefulness in a clinical setting.

7.3.1 The Importance of Clinical Cohorts

Clinical cohorts are extremely useful in examining the efficacy of diagnostic tools in a clinical setting, where they would ultimately be used. While clinical cohorts are not a population based cohort, they are still are more heterogeneous than the previously mentioned research cohorts. The patients in these cohorts usually come from a wider range of socioeconomic backgrounds, with more varying levels of education. Most importantly, clinical cohorts have more lenient inclusion criteria and do not omit participants based on comorbidities. As manly people with dementia do indeed have other disorders in addition, it is important to test diagnostic tools in this setting to ensure any tool is robust enough to not be influenced by other conditions.

Additionally, if diagnostic tools are to be used in memory clinics, they must be proficient at distinguishing different types of dementia. The memory clinic cohort offers the opportunity to observe diagnostic tools on a wide range of symptoms and dementia subtypes. Research cohorts such as ADNI and AddNeuroMed, only include healthy controls, MCI, and AD patients in any analyses, and do not provide the opportunity to examine different types of dementia.

While not all clinical cohorts will have connection with EHRs, this integration provides an opportunity to gather patient data beyond what would normally be collected in a research study. There may be information about lifestyle choices, or records from other clinics that may aid in research studies.

In addition to testing the accuracy of diagnostic tools, clinical cohorts provide the opportunity to test practicality, and the ease of implementation. Ensuring full and efficient integration of diagnostic tools is possible is just as important as accuracy testing.

7.4 Electronic Health Record Usage for Research Purposes

Both medical professionals and researchers have concluded that there is a very strong opportunity for studies with clinical cohorts and even population-wide research that may aid in bridging the translational gap between research and clinical practice through the use of sharing electronic health records (Jensen et al., 2012). Using EHR records allows investigation of clinical disorders without potential cohort biases such as those with the 'volunteer-gene'. This 'volunteer-gene' refers to people with inherent differences that make them more likely to volunteer for a research study (Sperling et al., 2011). Additionally, using EHRs may eliminate biases brought on by samples of convenience.

Integration of EHRs for research purposes may also aid in the implementation of longitudinal studies. As EHRs follow standard clinical care, there are no extra appointment requirements, and may result in less participant attenuation. Many patients may move hospitals, and therefore effectively 'drop-out', the wider catchment means that even with these subjects leaving, there will still be a substantial number of patients with follow-up data.

Finally, the application of EHR for research purposes extends far past the research completed in this thesis. In the case of MRI imaging, a myriad of mental health disorders, such as depression or psychosis, could benefit from EHR integration to monitor brain imaging, pharmacological treatments, and other cognitive therapies. Furthermore, EHRs can be integrated with various modalities, such as blood testing, which could further fuel research into blood based biomarkers.

7.5 LIMITATIONS

While this PhD discusses promising potentials for the future of dementia research, there are several limitations that must be addressed.

7.5.1 Clinical Cohort Samples

There are significant benefits for using a clinical cohort instead of a research based cohort, however clinical cohorts are still not full population samples. Clinical cohorts are subjected to bias as they may contain people who have better access to health care, or have more severe symptoms (Brodaty et al., 2014). Consistent with this, clinically referred MCI participants are more likely to be married and living independently than wider population of MCI patients (Barnhart et al., 1995; Farias, Mungas, Reed, Harvey, & DeCarli, 2009).

7.5.2 Lack of Consistency in Electronic Health Records and Memory Clinic Centres

As seen in this study, there are many challenges with EHR linkages. Many subjects in the BRC Memory Clinic Cohort, roughly 40%, were missing MMSE score in their electronic health records, and a number of them did not have a final diagnosis listed. This was not a challenge in these analyses, as the large number of participants to begin with meant there was still a decent sized cohort even despite of these missing records.

Additionally, while patients received their diagnoses in a generally close proximity to any diagnostic tests used in the analyses, not all patients received their diagnosis the same specified time (for example, 3 months after MRI scan). In the future, it would be beneficial to factor in how long to final diagnosis into analyses.

The South London and Maudsley Hospital (SLaM) has developed a standardised procedure for their memory clinics, however, this is not the case for the majority of the UK. There is often a lack of standardisation for diagnostic procedures, which may hinder EHR integration across various clinics.

7.5.3 Volumetric Studies in Alzheimer's Disease and Dementia

As previously mentioned, AD is a heterogenous disorder and can have several neuropathological presentations (Daniel Ferreira, Verhagen, et al., 2017). It has been found that potentially 17% of patients with AD do not exhibit hippocampal atrophy, and greater than 10% of those with AD do not experience atrophy at all. The diagnostic tests examined in this thesis may not apply to a portion of patients with AD, and therefore my hinder clinical applicability.

Additionally, hippocampal is not exclusive to AD, and can be found in other disorders such as depression (Taylor et al., 2014). This must be taken into consideration when testing and analysing diagnostic tools in dementia.

7.6 CONCLUSION

Automated measures, such as white matter hyperintensity measurements and automated volumetry reports, have the potential to increase efficiency in clinics and aid in the diagnostic process. The results of this thesis show these measures may be promising, and are still accurate in a clinical setting. More research needs to be done on effective transition to using these tools.

Additionally, this thesis has shown the promise of integrating EHRs for research purposes. There are a myriad of potential applications, and further work should be done to develop a more streamlined process.

REFERENCES

Aggleton, J. P. (2012). Multiple anatomical systems embedded within the primate medial temporal lobe: Implications for hippocampal function. *Neuroscience & Biobehavioral Reviews*, *36*(7), 1579–1596. https://doi.org/10.1016/j.neubiorev.2011.09.005

Aguilar, C., Westman, E., Muehlboeck, J.-S., Mecocci, P., Vellas, B., Tsolaki, M., … Wahlund, L.-O. (2013a). Different multivariate techniques for automated classification of MRI data in Alzheimer's disease and mild cognitive impairment. *Psychiatry Research: Neuroimaging*, *212*(2), 89–98. https://doi.org/10.1016/j.pscychresns.2012.11.005

Aguilar, C., Westman, E., Muehlboeck, J.-S., Mecocci, P., Vellas, B., Tsolaki, M., … Wahlund, L.-O. (2013b). Different multivariate techniques for automated classification of MRI data in Alzheimer's disease and mild cognitive impairment. *Psychiatry Research: Neuroimaging*, *212*(2), 89–98. https://doi.org/10.1016/j.pscychresns.2012.11.005

Ahmed, R. M., Paterson, R. W., Warren, J. D., Zetterberg, H., O'Brien, J. T., Fox, N. C., … Schott, J. M. (2014). Biomarkers in dementia: clinical utility and new directions. *Journal of Neurology, Neurosurgery, and Psychiatry*, *85*(12), 1426–1434. https://doi.org/10.1136/jnnp-2014-307662

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., … Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, *7*(3), 270–279. https://doi.org/10.1016/j.jalz.2011.03.008

Alexander, G. E., Chen, K., Pietrini, P., Rapoport, S. I., & Reiman, E. M. (2002). Longitudinal PET Evaluation of Cerebral Metabolic Decline in Dementia: A Potential Outcome Measure in Alzheimer's Disease Treatment Studies. *The American Journal of Psychiatry*, *159*(5), 738–745. https://doi.org/10.1176/appi.ajp.159.5.738

Alladi, S., Xuereb, J., Bak, T., Nestor, P., Knibb, J., Patterson, K., & Hodges, J. R. (2007). Focal cortical presentations of Alzheimer's disease. *Brain: A Journal of Neurology*, *130*(Pt 10), 2636–2645. https://doi.org/10.1093/brain/awm213

Allen, G., Barnard, H., McColl, R., Hester, A. L., Fields, J. A., Weiner, M. F., … Cullum, M. (2007). Reduced Hippocampal Functional Connectivity in Alzheimer Disease. *Archives of Neurology*, *64*(10), 1482–1487.

Alsop, D. C., Detre, J. A., & Grossman, M. (2000). Assessment of cerebral blood flow in Alzheimer's disease by spin-labeled magnetic resonance imaging. *Annals of Neurology*, *47*(1), 93–100.

Altman, D. G., & Bland, J. M. (1994a). Diagnostic tests. 1: Sensitivity and specificity. *BMJ : British Medical Journal*, *308*(6943), 1552.

Altman, D. G., & Bland, J. M. (1994b). Diagnostic tests 2: Predictive values. *BMJ : British Medical Journal*, *309*(6947), 102.

Altman, D. G., & Bland, J. M. (2009). Parametric v non-parametric methods for data analysis. *BMJ*, *338*, a3167. https://doi.org/10.1136/bmj.a3167

Alzheimer's Society. (2015, July). Dementia 2015: Aiming Higher to Transform Lives. Retrieved May 30, 2017, from https://www.alzheimers.org.uk/download/downloads/id/2700/dementia_2015_aiming_higher_to_transform_lives.pdf

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC.

Amlien, I. K., & Fjell, A. M. (2014). Diffusion tensor imaging of white matter degeneration in Alzheimer's disease and mild cognitive impairment. *Neuroscience*, *276*, 206–215. https://doi.org/10.1016/j.neuroscience.2014.02.017

Anderson, N. B., Bulatao, R. A., Cohen, B., & National Research Council (US) Panel on Race, E. (2004). *Ethnic Differences in Dementia and Alzheimer's Disease*. National Academies Press (US). Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK25535/

Arbabshirani, M. R., Plis, S., Sui, J., & Calhoun, V. D. (2016). Single subject prediction of brain disorders in neuroimaging: Promises and pitfalls. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2016.02.079

Arevalo-Rodriguez, I., Smailagic, N., Roqué I Figuls, M., Ciapponi, A., Sanchez-Perez, E., Giannakou, A., … Cullum, S. (2015). Mini-Mental State Examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI). *The Cochrane Database of Systematic Reviews*, (3), CD010783. https://doi.org/10.1002/14651858.CD010783.pub2

Arlt, S., Buchert, R., Spies, L., Eichenlaub, M., Lehmbeck, J. T., & Jahn, H. (2013). Association between fully automated MRI-based volumetry of different brain regions and neuropsychological test performance in patients with amnestic mild cognitive impairment and Alzheimer's disease. *European Archives of Psychiatry and Clinical Neuroscience*, *263*(4), 335–344. https://doi.org/10.1007/s00406-012-0350-7

Arndt, S., Cohen, G., Alliger, R. J., Swayze, V. W., & Andreasen, N. C. (1991). Problems with ratio and proportion measures of imaged cerebral structures. *Psychiatry Research*, *40*(1), 79–89.

Arvanitakis, Z., Leurgans, S. E., Barnes, L. L., Bennett, D. A., & Schneider, J. A. (2011). Microinfarct pathology, dementia, and cognitive systems. *Stroke*, *42*(3), 722–727. https://doi.org/10.1161/STROKEAHA.110.595082

Asllani, I., Habeck, C., Scarmeas, N., Borogovac, A., Brown, T. R., & Stern, Y. (2008). Multivariate and univariate analysis of continuous arterial spin labeling perfusion MRI in Alzheimer's disease.

Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism, *28*(4), 725–736. https://doi.org/10.1038/sj.jcbfm.9600570

Austin, M., Gray, K. R., Wolz, R., Marais, L., McLeish, K., & Hill, D. (2014). A Weighted Atrophy Index for Medial Temporal Lobe Assessment in Alzheimer's Disease. Presented at the Clinical Trials on Alzheimer's disease (CTAD), Philadelphia USA. Retrieved from http://marketing.ixico.info/acton/attachment/16534/f-0038/1/-/-/-/-/A%20Weighted%20Atrophy%20Index%20for%20Medial%20Temporal%20Lobe%20Assessment%20in%20Alzheimer%E2%80%99s%20Disease.pdf

Bamford, C., Eccles, M., Steen, N., & Robinson, L. (2007). Can primary care record review facilitate earlier diagnosis of dementia? *Family Practice*, *24*(2), 108–116. https://doi.org/10.1093/fampra/cml068

Barber, R., Scheltens, P., Gholkar, A., Ballard, C., McKeith, I., Ince, P., … O'Brien, J. (1999). White matter lesions on magnetic resonance imaging in dementia with Lewy bodies, Alzheimer's disease, vascular dementia, and normal aging. *Journal of Neurology, Neurosurgery & Psychiatry*, *67*(1), 66–72. https://doi.org/10.1136/jnnp.67.1.66

Barkhof, F. (Ed.). (2011). *Neuroimaging in dementia*. Heidelberg ; New York: Springer.

Barnes, J., Ridgway, G. R., Bartlett, J., Henley, S. M. D., Lehmann, M., Hobbs, N., … Fox, N. C. (2010). Head size, age and gender adjustment in MRI studies: a necessary nuisance? *NeuroImage*, *53*(4), 1244–1255. https://doi.org/10.1016/j.neuroimage.2010.06.025

Barnhart, R. L., van Belle, G., Edland, S. D., Kukull, W., Borson, S., Raskind, M., … Larson, E. (1995). Geographically overlapping Alzheimer's disease registries: comparisons and implications. *Journal of Geriatric Psychiatry and Neurology*, *8*(4), 203–208. https://doi.org/10.1177/089198879500800401

Barthel, H., Gertz, H.-J., Dresel, S., Peters, O., Bartenstein, P., Buerger, K., … Sabri, O. (2011). Cerebral amyloid-β PET with florbetaben (18F) in patients with Alzheimer's disease and healthy controls:

a multicentre phase 2 diagnostic study. *The Lancet Neurology*, *10*(5), 424–435. https://doi.org/10.1016/S1474-4422(11)70077-1

Bartzokis, G. (2004). Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. *Neurobiology of Aging*, *25*(1), 5-18-62.

Bartzokis, G., Lu, P. H., & Mintz, J. (2007). Human brain myelination and amyloid beta deposition in Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *3*(2), 122–125. https://doi.org/10.1016/j.jalz.2007.01.019

Bateman, R. J., Munsell, L. Y., Morris, J. C., Swarm, R., Yarasheski, K. E., & Holtzman, D. M. (2006). Human amyloid-beta synthesis and clearance rates as measured in cerebrospinal fluid in vivo. *Nature Medicine*, *12*(7), 856–861. https://doi.org/10.1038/nm1438

Beach, T. G., Monsell, S. E., Phillips, L. E., & Kukull, W. (2012). Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005-2010. *Journal of Neuropathology and Experimental Neurology*, *71*(4), 266–273. https://doi.org/10.1097/NEN.0b013e31824b211b

Benedictus, M. R., Binnewijzend, M. A. A., Kuijer, J. P. A., Steenwijk, M. D., Versteeg, A., Vrenken, H., … Prins, N. D. (2014). Brain volume and white matter hyperintensities as determinants of cerebral blood flow in Alzheimer's disease. *Neurobiology of Aging*, *35*(12), 2665–2670. https://doi.org/10.1016/j.neurobiolaging.2014.06.001

Bennett, D. A., Schneider, J. A., Arvanitakis, Z., & Wilson, R. S. (2012). Overview and findings from the religious orders study. *Current Alzheimer Research*, *9*(6), 628–645.

Bennett, D. A., Schneider, J. A., Buchman, A. S., Barnes, L. L., Boyle, P. A., & Wilson, R. S. (2012). Overview and findings from the rush Memory and Aging Project. *Current Alzheimer Research*, *9*(6), 646–663.

Bennett, D. A., Wilson, R. S., Arvanitakis, Z., Boyle, P. A., de Toledo-Morrell, L., & Schneider, J. A. (2013). Selected findings from the Religious Orders Study and Rush Memory and Aging Project. *Journal of Alzheimer's Disease: JAD*, *33 Suppl 1*, S397-403. https://doi.org/10.3233/JAD-2012-129007

Bilello, M., Doshi, J., Nabavizadeh, S. A., Toledo, J. B., Erus, G., Xie, S. X., … Davatzikos, C. (2015). Correlating Cognitive Decline with White Matter Lesion and Brain Atrophy MRI Measurements in Alzheimer's Disease. *Journal of Alzheimer's Disease : JAD*, *48*(4), 987–994. https://doi.org/10.3233/JAD-150400

Biomarkers Definitions Working Group. (2001). Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clinical Pharmacology and Therapeutics*, *69*(3), 89–95. https://doi.org/10.1067/mcp.2001.113989

Bischof, G. N., Endepols, H., van Eimeren, T., & Drzezga, A. (2017). Tau-imaging in neurodegeneration. *Methods*. https://doi.org/10.1016/j.ymeth.2017.08.003

Biswal, B. B., Van Kylen, J., & Hyde, J. S. (1997). Simultaneous assessment of flow and BOLD signals in resting-state functional connectivity maps. *NMR in Biomedicine*, *10*(4–5), 165–170.

Black, S., Gao, F., & Bilbao, J. (2009). Understanding white matter disease: imaging-pathological correlations in vascular cognitive impairment. *Stroke*, *40*(3 Suppl), S48-52. https://doi.org/10.1161/STROKEAHA.108.537704

Blennow, K., de Leon, M. J., & Zetterberg, H. (2006). Alzheimer's disease. *The Lancet*, *368*(9533), 387–403. https://doi.org/10.1016/S0140-6736(06)69113-7

Blennow, K., Hampel, H., Weiner, M., & Zetterberg, H. (2010). Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. *Nature Reviews Neurology*, *6*(3), 131–144. https://doi.org/10.1038/nrneurol.2010.4

Blennow, K., Wallin, A., Ågren, H., Spenger, C., Siegfried, J., & Vanmechelen, E. (1995). tau protein in cerebrospinal fluid. *Molecular and Chemical Neuropathology*, *26*(3), 231–245. https://doi.org/10.1007/BF02815140

Blennow, K., Zetterberg, H., Minthon, L., Lannfelt, L., Strid, S., Annas, P., … Andreasen, N. (2007). Longitudinal stability of CSF biomarkers in Alzheimer's disease. *Neuroscience Letters*, *419*(1), 18–22. https://doi.org/10.1016/j.neulet.2007.03.064

Blom, E. S., Giedraitis, V., Zetterberg, H., Fukumoto, H., Blennow, K., Hyman, B. T., … Ingelsson, M. (2009). Rapid Progression from Mild Cognitive Impairment to Alzheimer's Disease in Subjects with Elevated Levels of Tau in Cerebrospinal Fluid and the APOE ε4/ε4 Genotype. *Dementia and Geriatric Cognitive Disorders*, *27*(5), 458–464. https://doi.org/10.1159/000216841

Blumenthal, D. (2010). Launching HITECH. *The New England Journal of Medicine*, *362*(5), 382–385. https://doi.org/10.1056/NEJMp0912825

Boccardi, M., Ganzola, R., Bocchetta, M., Pievani, M., Redolfi, A., Bartzokis, G., … Frisoni, G. B. (2011). Survey of Protocols for the Manual Segmentation of the Hippocampus: Preparatory Steps Towards a Joint EADC-ADNI Harmonized Protocol. *Journal of Alzheimer's Disease : JAD*, *26*(0 3). https://doi.org/10.3233/JAD-2011-0004

Boise, L., Morgan, D. L., Kaye, J., & Camicioli, R. (1999). Delays in the diagnosis of dementia: Perspectives of family caregivers. *American Journal of Alzheimer's Disease*, *14*(1), 20–26. https://doi.org/10.1177/153331759901400101

Bokde, A. L. W., Karmann, M., Teipel, S. J., Born, C., Lieb, M., Reiser, M. F., … Hampel, H. (2009). Decreased activation along the dorsal visual pathway after a 3-month treatment with galantamine in mild Alzheimer disease: a functional magnetic resonance imaging study. *Journal of Clinical Psychopharmacology*, *29*(2), 147–156. https://doi.org/10.1097/JCP.0b013e31819a8f2e

Bonte, F. J., Weiner, M. F., Bigio, E. H., & White, C. L. (1997). Brain blood flow in the dementias: SPECT with histopathologic correlation in 54 patients. *Radiology*, *202*(3), 793–797. https://doi.org/10.1148/radiology.202.3.9051035

Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica*, *82*(4), 239–259.

Braak, H., Braak, E., & Bohl, J. (1993). Staging of Alzheimer-related cortical destruction. *European Neurology*, *33*(6), 403–408.

Bradford, A., Kunik, M. E., Schulz, P., Williams, S. P., & Singh, H. (2009). Missed and Delayed Diagnosis of Dementia in Primary Care: Prevalence and Contributing Factors. *Alzheimer Disease and Associated Disorders*, *23*(4), 306–314. https://doi.org/10.1097/WAD.0b013e3181a6bebc

Brewer, J. B., Magda, S., Airriess, C., & Smith, M. E. (2009). Fully-automated quantification of regional brain volumes for improved detection of focal atrophy in Alzheimer disease. *AJNR. American Journal of Neuroradiology*, *30*(3), 578–580. https://doi.org/10.3174/ajnr.A1402

Brodaty, H., Mothakunnel, A., de Vel-Palumbo, M., Ames, D., Ellis, K. A., Reppermund, S., … Sachdev, P. S. (2014). Influence of population versus convenience sampling on sample characteristics in studies of cognitive aging. *Annals of Epidemiology*, *24*(1), 63–71. https://doi.org/10.1016/j.annepidem.2013.10.005

Brookmeyer, R., Johnson, E., Ziegler-Graham, K., & Arrighi, H. M. (2007). Forecasting the global burden of Alzheimer's disease. *Alzheimer's & Dementia*, *3*(3), 186–191. https://doi.org/10.1016/j.jalz.2007.04.381

Brun, A., & Englund, E. (1986). A white matter disorder in dementia of the Alzheimer type: A pathoanatomical study. *Annals of Neurology*, *19*(3), 253–262. https://doi.org/10.1002/ana.410190306

Buckner, R. L., Snyder, A. Z., Shannon, B. J., LaRossa, G., Sachs, R., Fotenos, A. F., … Mintun, M. A. (2005). Molecular, Structural, and Functional Characterization of Alzheimer's Disease: Evidence for a Relationship between Default Activity, Amyloid, and Memory. *Journal of Neuroscience*, *25*(34), 7709–7717. https://doi.org/10.1523/JNEUROSCI.2177-05.2005

Buerger, K., Ewers, M., Pirttilä, T., Zinkowski, R., Alafuzoff, I., Teipel, S. J., … Hampel, H. (2006). CSF phosphorylated tau protein correlates with neocortical neurofibrillary pathology in Alzheimer's disease. *Brain*, *129*(11), 3035–3041. https://doi.org/10.1093/brain/awl269

Burns, A., Wilkinson, A., & Peachey, S. (2014). Best Practice in Memory Services: Learning from across England. Retrieved June 1, 2017, from https://www.england.nhs.uk/wp-content/uploads/2014/12/memory-clinics-final.pdf

Busse, A., Hensel, A., Guhne, U., Angermeyer, M. C., & Riedel-Heller, S. G. (2006). Mild cognitive impairment: Long-term course of four clinical subtypes. *Neurology*, *67*(12), 2176–2185. https://doi.org/10.1212/01.wnl.0000249117.23318.e1

Cacace, R., Sleegers, K., & Van Broeckhoven, C. (2016). Molecular genetics of early-onset Alzheimer's disease revisited. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *12*(6), 733–748. https://doi.org/10.1016/j.jalz.2016.01.012

Caixeta, L., Soares, V. L., & Soares, C. D. (2009). Absence of MRI exams in epidemiological studies can leads to clinical overdiagnosis of Alzheimer's disease and underdiagnosis of vascular dementia. *Arquivos De Neuro-Psiquiatria*, *67*(2A), 369–370.

Callard, F., Broadbent, M., Denis, M., Hotopf, M., Soncul, M., Wykes, T., … Stewart, R. (2014). Developing a new model for patient recruitment in mental health services: a cohort study using Electronic Health Records. *BMJ Open*, *4*(12), e005654. https://doi.org/10.1136/bmjopen-2014-005654

Camus, V., Payoux, P., Barré, L., Desgranges, B., Voisin, T., Tauber, C., … Guilloteau, D. (2012). Using PET with 18F-AV-45 (florbetapir) to quantify brain amyloid load in a clinical environment. *European*

Journal of Nuclear Medicine and Molecular Imaging, *39*(4), 621–631. https://doi.org/10.1007/s00259-011-2021-8

Celone, K. A., Calhoun, V. D., Dickerson, B. C., Atri, A., Chua, E. F., Miller, S. L., … Sperling, R. A. (2006). Alterations in Memory Networks in Mild Cognitive Impairment and Alzheimer's Disease: An Independent Component Analysis. *Journal of Neuroscience*, *26*(40), 10222–10231. https://doi.org/10.1523/JNEUROSCI.2250-06.2006

Chao, L. L., Schuff, N., Kramer, J. H., Du, A. T., Capizzano, A. A., O'Neill, J., … Weiner, M. W. (2005). Reduced medial temporal lobe N-acetylaspartate in cognitively impaired but nondemented patients. *Neurology*, *64*(2), 282–289. https://doi.org/10.1212/01.WNL.0000149638.45635.FF

Cheng, Y.-W., Chen, T.-F., Cheng, T.-W., Lai, Y.-M., Hua, M.-S., Chen, Y.-F., & Chiu, M.-J. (2015). Hippocampal atrophy but not white-matter changes predicts the long-term cognitive response to cholinesterase inhibitors in Alzheimer's disease. *Alzheimer's Research & Therapy*, *7*. https://doi.org/10.1186/s13195-015-0155-9

Chételat, G. (2013). Alzheimer disease: Aβ-independent processes—rethinking preclinical AD. *Nature Reviews Neurology*, *9*(3), 123–124. https://doi.org/10.1038/nrneurol.2013.21

Chetelat, G., Desgranges, B., de la Sayette, V., Viader, F., Berkouk, K., Landeau, B., … Eustache, F. (2003). Dissociating atrophy and hypometabolism impact on episodic memory in mild cognitive impairment. *Brain: A Journal of Neurology*, *126*(Pt 9), 1955–1967. https://doi.org/10.1093/brain/awg196

Chételat, G., Eustache, F., Viader, F., De La Sayette, V., Pélerin, A., Mézenge, F., … Desgranges, B. (2005). FDG-PET measurement is more accurate than neuropsychological assessments to predict global cognitive deterioration in patients with mild cognitive impairment. *Neurocase*, *11*(1), 14–25. https://doi.org/10.1080/13554790490896938

Chien, D. T., Bahri, S., Szardenings, A. K., Walsh, J. C., Mu, F., Su, M.-Y., … Kolb, H. C. (2013). Early clinical PET imaging results with the novel PHF-tau radioligand [F-18]-T807. *Journal of Alzheimer's Disease: JAD*, *34*(2), 457–468. https://doi.org/10.3233/JAD-122059

Cho, H., Choi, J. Y., Hwang, M. S., Kim, Y. J., Lee, H. M., Lee, H. S., … Lyoo, C. H. (2016). In vivo cortical spreading pattern of tau and amyloid in the Alzheimer disease spectrum. *Annals of Neurology*, *80*(2), 247–258. https://doi.org/10.1002/ana.24711

Cho, H., Kwon, J.-H., & Seo, H.-J. (2009). Medial temporal lobe atrophy in vascular dementia: Visual temporal lobe rating scale. *Archives of Gerontology and Geriatrics*, *48*(3), 415–418. https://doi.org/10.1016/j.archger.2008.03.014

Chui, H. C., & Ramirez-Gomez, L. (2015). Clinical and imaging features of mixed Alzheimer and vascular pathologies. *Alzheimer's Research & Therapy*, *7*(1). https://doi.org/10.1186/s13195-015-0104-7

Clark, C. M., Schneider, J. A., Bedell, B. J., Beach, T. G., Bilker, W. B., Mintun, M. A., … AV45-A07 Study Group. (2011). Use of florbetapir-PET for imaging beta-amyloid pathology. *JAMA*, *305*(3), 275–283. https://doi.org/10.1001/jama.2010.2008

Coart, E., Barrado, L. G., Duits, F. H., Scheltens, P., van der Flier, W. M., Teunissen, C. E., … Alzheimer's Disease Neuroimaging Initiative. (2015). Correcting for the Absence of a Gold Standard Improves Diagnostic Accuracy of Biomarkers in Alzheimer's Disease. *Journal of Alzheimer's Disease: JAD*, *46*(4), 889–899. https://doi.org/10.3233/JAD-142886

Cohen, A. D., & Klunk, W. E. (2014). Early detection of Alzheimer's disease using PiB and FDG PET. *Neurobiology of Disease*. https://doi.org/10.1016/j.nbd.2014.05.001

Coiera, E. (2009). Building a National Health IT System from the middle out. *Journal of the American Medical Informatics Association: JAMIA*, *16*(3), 271–273. https://doi.org/10.1197/jamia.M3183

Coleman, R. E. (2005). Positron Emission Tomography Diagnosis of Alzheimer's Disease. *Neuroimaging Clinics of North America*, *15*(4), 837–846. https://doi.org/10.1016/j.nic.2005.09.007

Consensus Report of the Working Group on: “Molecular and Biochemical Markers of Alzheimer’s Disease” 1 2. (1998). *Neurobiology of Aging*, *19*(2), 109–116. https://doi.org/10.1016/S0197-4580(98)00022-0

Corder, E. H., Saunders, A. M., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Small, G. W., … Pericak-Vance, M. A. (1993). Gene Dose of Apolipoprotein E Type 4 Allele and the Risk of Alzheimer’s Disease in Late Onset Families. *Science*, *261*(5123), 921–923.

Corrada, M. M., Sonnen, J. A., Kim, R. C., & Kawas, C. H. (2016). Microinfarcts are common and strongly related to dementia in the oldest-old: The 90+ study. *Alzheimer’s & Dementia: The Journal of the Alzheimer’s Association*, *12*(8), 900–908. https://doi.org/10.1016/j.jalz.2016.04.006

Cselényi, Z., Jönhagen, M. E., Forsberg, A., Halldin, C., Julin, P., Schou, M., … Farde, L. (2012). Clinical validation of 18F-AZD4694, an amyloid-β-specific PET radioligand. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine*, *53*(3), 415–424. https://doi.org/10.2967/jnumed.111.094029

Cui, Y., Liu, B., Luo, S., Zhen, X., Fan, M., Liu, T., … Alzheimer’s Disease Neuroimaging Initiative. (2011). Identification of conversion from mild cognitive impairment to Alzheimer’s disease using multivariate predictors. *PloS One*, *6*(7), e21896. https://doi.org/10.1371/journal.pone.0021896

Cuingnet, R., Gerardin, E., Tessieras, J., Auzias, G., Lehéricy, S., Habert, M.-O., … Colliot, O. (2011). Automatic classification of patients with Alzheimer’s disease from structural MRI: A comparison of ten methods using the ADNI database. *NeuroImage*, *56*(2), 766–781. https://doi.org/10.1016/j.neuroimage.2010.06.013

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis. I. Segmentation and surface reconstruction. *NeuroImage*, *9*(2), 179–194. https://doi.org/10.1006/nimg.1998.0395

Dale, A. M., & Sereno, M. I. (1993). Improved Localizadon of Cortical Activity by Combining EEG and MEG with MRI Cortical Surface Reconstruction: A Linear Approach. *Journal of Cognitive Neuroscience*, *5*(2), 162–176. https://doi.org/10.1162/jocn.1993.5.2.162

Damangir, S., Manzouri, A., Oppedal, K., Carlsson, S., Firbank, M. J., Sonnesyn, H., … Spulber, G. (2012). Multispectral MRI segmentation of age related white matter changes using a cascade of support vector machines. *Journal of the Neurological Sciences*, *322*(1–2), 211–216. https://doi.org/10.1016/j.jns.2012.07.064

Damoiseaux, J. S., Rombouts, S., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences*, *103*(37), 13848–13853.

Davies, L., Wolska, B., Hilbich, C., Multhaup, G., Martins, R., Simms, G., … Masters, C. L. (1988). A4 amyloid protein deposition and the diagnosis of Alzheimer's disease: prevalence in aged brains determined by immunocytochemistry compared with conventional neuropathologic techniques. *Neurology*, *38*(11), 1688–1693.

de Flores, R., La Joie, R., & Chételat, G. (2015). Structural imaging of hippocampal subfields in healthy aging and Alzheimer's disease. *Neuroscience*, *309*, 29–50. https://doi.org/10.1016/j.neuroscience.2015.08.033

de Leon, M. J., Mosconi, L., Blennow, K., DeSanti, S., Zinkowski, R., Mehta, P. D., … Rusinek, H. (2007). Imaging and CSF studies in the preclinical diagnosis of Alzheimer's disease. *Annals of the New York Academy of Sciences*, *1097*, 114–145. https://doi.org/10.1196/annals.1379.012

De Meyer, G., Shapiro, F., Vanderstichele, H., Vanmechelen, E., Engelborghs, S., De Deyn, P. P., … Alzheimer's Disease Neuroimaging Initiative. (2010). Diagnosis-independent Alzheimer disease biomarker signature in cognitively normal elderly people. *Archives of Neurology*, *67*(8), 949–956. https://doi.org/10.1001/archneurol.2010.179

De Reuck, J., Deramecourt, V., Cordonnier, C., Pasquier, F., Leys, D., Maurage, C.-A., & Bordet, R. (2016). The incidence of post-mortem neurodegenerative and cerebrovascular pathology in mixed dementia. *Journal of the Neurological Sciences*, *366*, 164–166. https://doi.org/10.1016/j.jns.2016.05.021

de Vugt, M. E., & Verhey, F. R. J. (2013). The impact of early dementia diagnosis and intervention on informal caregivers. *Progress in Neurobiology*, *110*, 54–62. https://doi.org/10.1016/j.pneurobio.2013.04.005

DeCarli, C., Frisoni, G. B., Clark, C. M., Harvey, D., Grundman, M., Petersen, R. C., … Alzheimer's Disease Cooperative Study Group. (2007). Qualitative estimates of medial temporal atrophy as a predictor of progression from mild cognitive impairment to dementia. *Archives of Neurology*, *64*(1), 108–115. https://doi.org/10.1001/archneur.64.1.108

DeCarli, C., Miller, B. L., Swan, G. E., Reed, T., Wolf, P. A., & Carmelli, D. (2001). Cerebrovascular and brain morphologic correlates of mild cognitive impairment in the National Heart, Lung, and Blood Institute Twin Study. *Archives of Neurology*, *58*(4), 643–647.

Deeks, J. J., & Altman, D. G. (2004). Diagnostic tests 4: likelihood ratios. *BMJ : British Medical Journal*, *329*(7458), 168–169.

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., … Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021

Devanand, D. P., Jacobs, D. M., Tang, M. X., Del Castillo-Castaneda, C., Sano, M., Marder, K., … Stern, Y. (1997). The course of psychopathologic features in mild to moderate Alzheimer disease. *Archives of General Psychiatry*, *54*(3), 257–263.

Diagnoses in the UK. (2015). Retrieved May 31, 2017, from https://www.dementiastatistics.org/statistics/diagnoses-in-the-uk/

Dougall, N. J., Bruggink, S., & Ebmeier, K. P. (2004). Systematic review of the diagnostic accuracy of 99mTc-HMPAO-SPECT in dementia. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *12*(6), 554–570. https://doi.org/10.1176/appi.ajgp.12.6.554

Drzezga, A., Grimmer, T., Riemenschneider, M., Lautenschlager, N., Siebner, H., Alexopoulus, P., … Kurz, A. (2005). Prediction of individual clinical outcome in MCI by means of genetic assessment and (18)F-FDG PET. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine*, *46*(10), 1625–1632.

Drzezga, A., Lautenschlager, N., Siebner, H., Riemenschneider, M., Willoch, F., Minoshima, S., … Kurz, A. (2003). Cerebral metabolic changes accompanying conversion of mild cognitive impairment into Alzheimer's disease: a PET follow-up study. *European Journal of Nuclear Medicine and Molecular Imaging*, *30*(8), 1104–1113. https://doi.org/10.1007/s00259-003-1194-1

Du, A.-T., Schuff, N., Chao, L. L., Kornak, J., Ezekiel, F., Jagust, W. J., … Weiner, M. W. (2005). White matter lesions are associated with cortical atrophy more than entorhinal and hippocampal atrophy. *Neurobiology of Aging*, *26*(4), 553–559. https://doi.org/10.1016/j.neurobiolaging.2004.05.002

Duara, R., Loewenstein, D. A., Potter, E., Appel, J., Greig, M. T., Urs, R., … Barker, W. (2008). Medial temporal lobe atrophy on MRI scans and the diagnosis of Alzheimer disease. *Neurology*, *71*(24), 1986–1992.

Duara, R. M., Loewenstein, D. A. P., Shen, Q. P., Barker, W., Varon, D. M., Greig, M. T. M., … Potter, H. P. (2013). The utility of age-specific cut-offs for visual rating of medial temporal atrophy in

classifying Alzheimer's disease, MCI and cognitively normal elderly subjects. *Frontiers in Aging Neuroscience*, *5*, 47. https://doi.org/10.3389/fnagi.2013.00047

Dubois, B., Feldman, H. H., Jacova, C., DeKosky, S. T., Barberger-Gateau, P., Cummings, J., … Jicha, G. (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria. *The Lancet Neurology*, *6*(8), 734–746.

Dubois, B., Hampel, H., Feldman, H. H., Scheltens, P., Aisen, P., Andrieu, S., … Jack Jr, C. R. (2016). Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. *Alzheimer's & Dementia*, *12*(3), 292–323. https://doi.org/10.1016/j.jalz.2016.02.002

Dubois, B., Padovani, A., Scheltens, P., Rossi, A., & Dell'Agnello, G. (2016). Timely Diagnosis for Alzheimer's Disease: A Literature Review on Benefits and Challenges. *Journal of Alzheimer's Disease*, *49*(3), 617–631. https://doi.org/10.3233/JAD-150692

Duchesne, S., Valdivia, F., Robitaille, N., Mouiha, A., Valdivia, F. A., Bocchetta, M., … EADC-ADNI Working Group on The Harmonized Protocol for Manual Hippocampal Segmentation and for the Alzheimer's Disease Neuroimaging Initiative. (2015). Manual segmentation qualification platform for the EADC-ADNI harmonized protocol for hippocampal segmentation project. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *11*(2), 161–174. https://doi.org/10.1016/j.jalz.2015.01.002

Dukart, J., Schroeter, M. L., Mueller, K., & Alzheimer's Disease Neuroimaging Initiative. (2011). Age correction in dementia--matching to a healthy brain. *PloS One*, *6*(7), e22193. https://doi.org/10.1371/journal.pone.0022193

Eckerström, C., Olsson, E., Klasson, N., Bjerke, M., Göthlin, M., Jonsson, M., … Edman, A. (2011). High white matter lesion load is associated with hippocampal atrophy in mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders*, *31*(2), 132–138. https://doi.org/10.1159/000323014

Engedal, K., Brækhus, A., Andreassen, O. A., & Nakstad, P. H. (2012). Diagnosis of dementia--automatic quantification of brain structures. *Tidsskrift for Den Norske Laegeforening: Tidsskrift for Praktisk Medicin, Ny Raekke*, *132*(15), 1747–1751. https://doi.org/10.4045/tidsskr.12.0148

Eriksson, L., Byrne, T., Johansson, E., Trygg, J., & Vikström, C. (2013). *Multi- and Megavariate Data Analysis Basic Principles and Applications*. Umetrics Academy.

Eriksson, L., Johansson, E., Kettaneh-Wold, N., Trygg, J., Wikstrom, C., & Wold, S. (2006). *Multi- and megavariate data analysis (Part 1 - Basic Principals and Applications)* (2nd ed.). Umea: Umetrics AB.

Falahati, F., Fereshtehnejad, S.-M., Religa, D., Wahlund, L.-O., Westman, E., & Eriksdotter, M. (2015). The use of MRI, CT and lumbar puncture in dementia diagnostics: data from the SveDem Registry. *Dementia and Geriatric Cognitive Disorders*, *39*(1–2), 81–91. https://doi.org/10.1159/000366194

Falahati, F., Ferreira, D., Muehlboeck, J.-S., Eriksdotter, M., Simmons, A., Wahlund, L.-O., & Westman, E. (2017). Monitoring disease progression in mild cognitive impairment: Associations between atrophy patterns, cognition, APOE and amyloid. *NeuroImage: Clinical*. https://doi.org/10.1016/j.nicl.2017.08.014

Falahati, F., Ferreira, D., Soininen, H., Mecocci, P., Vellas, B., Tsolaki, M., … AddNeuroMed consortium and the Alzheimer's Disease Neuroimaging Initiative. (2016). The Effect of Age Correction on Multivariate Classification in Alzheimer's Disease, with a Focus on the Characteristics of Incorrectly and Correctly Classified Subjects. *Brain Topography*, *29*(2), 296–307. https://doi.org/10.1007/s10548-015-0455-1

Falahati, F., Westman, E., & Simmons, A. (In Press). Multivariate Data Analysis and Machine Learning in Alzheimer's Disease with a Focus on Structural Magnetic Resonance Imaging. *Journal of Alzheimer's Disease*. https://doi.org/10.3233/JAD-131928

Falahati, F., Westman, E., & Simmons, A. (2014). Multivariate Data Analysis and Machine Learning in Alzheimer's Disease with a Focus on Structural Magnetic Resonance Imaging. *Journal of Alzheimer's Disease*, *41*(3), 685–708. https://doi.org/10.3233/JAD-131928

Farias, S. T., Mungas, D., Reed, B. R., Harvey, D., & DeCarli, C. (2009). Progression of mild cognitive impairment to dementia in clinic- vs community-based cohorts. *Archives of Neurology*, *66*(9), 1151–1157. https://doi.org/10.1001/archneurol.2009.106

Fazekas, F., Chawluk, J., Alavi, A., Hurtig, H., & Zimmerman, R. (1987). MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *American Journal of Roentgenology*, *149*(2), 351–356. https://doi.org/10.2214/ajr.149.2.351

Fernandes, A. C., Cloete, D., Broadbent, M. T. M., Hayes, R. D., Chang, C.-K., Jackson, R. G., … Callard, F. (2013). Development and evaluation of a de-identification procedure for a case register sourced from mental health electronic records. *BMC Medical Informatics and Decision Making*, *13*, 71. https://doi.org/10.1186/1472-6947-13-71

Ferreira, D., Cavallin, L., Larsson, E.-M., Muehlboeck, J.-S., Mecocci, P., Vellas, B., … AddNeuroMed consortium and the Alzheimer's Disease Neuroimaging Initiative. (2015). Practical cut-offs for visual rating scales of medial temporal, frontal and posterior atrophy in Alzheimer's disease and mild cognitive impairment. *Journal of Internal Medicine*, *278*(3), 277–290. https://doi.org/10.1111/joim.12358

Ferreira, D., Falahati, F., Linden, C., Buckley, R. F., Ellis, K. A., Savage, G., … Westman, E. (2017). A "Disease Severity Index" to identify individuals with Subjective Memory Decline who will progress to mild cognitive impairment or dementia. *Scientific Reports*, *7*. https://doi.org/10.1038/srep44368

Ferreira, D., Verhagen, C., Hernández-Cabrera, J. A., Cavallin, L., Guo, C.-J., Ekman, U., … Westman, E. (2017). Distinct subtypes of Alzheimer's disease based on patterns of brain atrophy: longitudinal trajectories and clinical applications. *Scientific Reports*, *7*. https://doi.org/10.1038/srep46263

Fiford, C. M., Manning, E. N., Bartlett, J. W., Cash, D. M., Malone, I. B., Ridgway, G. R., … Barnes, J. (2017). White matter hyperintensities are associated with disproportionate progressive hippocampal atrophy. *Hippocampus*, *27*(3), 249–262. https://doi.org/10.1002/hipo.22690

Filipek, P. A., Richelme, C., Kennedy, D. N., & Caviness, V. S. (1994). The young adult human brain: an MRI-based morphometric analysis. *Cerebral Cortex (New York, N.Y.: 1991)*, *4*(4), 344–360.

Filippini, N., MacIntosh, B. J., Hough, M. G., Goodwin, G. M., Frisoni, G. B., Smith, S. M., … Mackay, C. E. (2009). Distinct patterns of brain activity in young carriers of the APOE-ε4 allele. *Proceedings of the National Academy of Sciences*, *106*(17), 7209–7214.

Fischl, B. (2012). FreeSurfer. *NeuroImage*, *62*(2), 774–781. https://doi.org/10.1016/j.neuroimage.2012.01.021

Fischl, B., & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(20), 11050–11055. https://doi.org/10.1073/pnas.200033797

Fischl, B., Liu, A., & Dale, A. M. (2001). Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. *IEEE Transactions on Medical Imaging*, *20*(1), 70–80. https://doi.org/10.1109/42.906426

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., … Dale, A. M. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*, *33*(3), 341–355.

Fischl, B., Salat, D. H., van der Kouwe, A. J. W., Makris, N., Ségonne, F., Quinn, B. T., & Dale, A. M. (2004). Sequence-independent segmentation of magnetic resonance images. *NeuroImage*, *23 Suppl 1*, S69-84. https://doi.org/10.1016/j.neuroimage.2004.07.016

Fischl, B., Sereno, M. I., Tootell, R. B., & Dale, A. M. (1999). High-resolution intersubject averaging and a coordinate system for the cortical surface. *Human Brain Mapping*, *8*(4), 272–284.

Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Ségonne, F., Salat, D. H., … Dale, A. M. (2004). Automatically parcellating the human cerebral cortex. *Cerebral Cortex (New York, N.Y.: 1991)*, *14*(1), 11–22.

Fleisher, A. S., Chen, K., Liu, X., Roontiva, A., Thiyyagura, P., Ayutyanont, N., … Reiman, E. M. (2011). Using positron emission tomography and florbetapir F18 to image cortical amyloid in patients with mild cognitive impairment or dementia due to Alzheimer disease. *Archives of Neurology*, *68*(11), 1404–1411. https://doi.org/10.1001/archneurol.2011.150

Forman, M. S., Mufson, E. J., Leurgans, S., Pratico, D., Joyce, S., Leight, S., … Trojanowski, J. Q. (2007). Cortical biochemistry in MCI and Alzheimer disease: lack of correlation with clinical diagnosis. *Neurology*, *68*(10), 757–763. https://doi.org/10.1212/01.wnl.0000256373.39415.b1

Frisoni, G. B., Fox, N. C., Jack, C. R., Scheltens, P., & Thompson, P. M. (2010). The clinical use of structural MRI in Alzheimer disease. *Nature Reviews. Neurology*, *6*(2), 67–77. https://doi.org/10.1038/nrneurol.2009.215

Frisoni, G. B., Jack, C. R., Bocchetta, M., Bauer, C., Frederiksen, K. S., Liu, Y., … EADC-ADNI Working Group on The Harmonized Protocol for Manual Hippocampal Volumetry and for the Alzheimer's Disease Neuroimaging Initiative. (2015). The EADC-ADNI Harmonized Protocol for manual hippocampal segmentation on magnetic resonance: evidence of validity. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *11*(2), 111–125. https://doi.org/10.1016/j.jalz.2014.05.1756

Frisoni, G., Testa, C., Zorzan, A., Sabattoli, F., Beltramello, A., Soininen, H., & Laakso, M. (2002). Detection of grey matter loss in mild Alzheimer's disease with voxel based morphometry. *Journal of Neurology, Neurosurgery, and Psychiatry*, *73*(6), 657–664. https://doi.org/10.1136/jnnp.73.6.657

Fukutani, Y., Cairns, N. J., Shiozawa, M., Sasaki, K., Sudo, S., Isaki, K., & Lantos, P. L. (2000). Neuronal loss and neurofibrillary degeneration in the hippocampal cortex in late-onset sporadic Alzheimer's disease. *Psychiatry and Clinical Neurosciences*, *54*(5), 523–529. https://doi.org/10.1046/j.1440-1819.2000.00747.x

Furst, A. J., Rabinovici, G. D., Rostomian, A. H., Steed, T., Alkalay, A., Racine, C., … Jagust, W. J. (2012). Cognition, glucose metabolism and amyloid burden in Alzheimer's disease. *Neurobiology of Aging*, *33*(2), 215–225. https://doi.org/10.1016/j.neurobiolaging.2010.03.011

Galton, C., Gomez-Anson, B., Antoun, N., Scheltens, P., Patterson, K., Graves, M., … Hodges, J. (2001). Temporal lobe rating scale: application to Alzheimer's disease and frontotemporal dementia. *Journal of Neurology, Neurosurgery & Psychiatry*, *70*, 165–173.

Gandhi, T. K., Kachalia, A., Thomas, E. J., Puopolo, A. L., Yoon, C., Brennan, T. A., & Studdert, D. M. (2006). Missed and delayed diagnoses in the ambulatory setting: a study of closed malpractice claims. *Annals of Internal Medicine*, *145*(7), 488–496.

Gattringer, T., Enzinger, C., Ropele, S., Gorani, F., Petrovic, K. E., Schmidt, R., & Fazekas, F. (2012). Vascular Risk Factors, White Matter Hyperintensities and Hippocampal Volume in Normal Elderly Individuals. *Dementia and Geriatric Cognitive Disorders*, *33*(1), 29–34. https://doi.org/10.1159/000336052

Gaugler, J. E., Ascher-Svanum, H., Roth, D. L., Fafowora, T., Siderowf, A., & Beach, T. G. (2013). Characteristics of patients misdiagnosed with Alzheimer's disease and their medication use: an

analysis of the NACC-UDS database. *BMC Geriatrics*, *13*, 137. https://doi.org/10.1186/1471-2318-13-137

Genin, E., Hannequin, D., Wallon, D., Sleegers, K., Hiltunen, M., Combarros, O., … Campion, D. (2011). APOE and Alzheimer disease: a major gene with semi-dominant inheritance. *Molecular Psychiatry*, *16*(9), 903–907. https://doi.org/10.1038/mp.2011.52

Geroldi, C., Laakso, M. P., DeCarli, C., Beltramello, A., Bianchetti, A., Soininen, H., … Frisoni, G. B. (2000). Apolipoprotein E genotype and hippocampal asymmetry in Alzheimer's disease: a volumetric MRI study. *Journal of Neurology, Neurosurgery, and Psychiatry*, *68*(1), 93–96.

Getsios, D., Blume, S., Ishak, K. J., Maclaine, G., & Hernández, L. (2012). An economic evaluation of early assessment for Alzheimer's disease in the United Kingdom. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *8*(1), 22–30. https://doi.org/10.1016/j.jalz.2010.07.001

Gibson, E., Gao, F., Black, S. E., & Lobaugh, N. J. (2010). Automatic segmentation of white matter hyperintensities in the elderly using FLAIR images at 3T. *Journal of Magnetic Resonance Imaging*, *31*(6), 1311–1322. https://doi.org/10.1002/jmri.22004

Goldman, M., Seigneuret, N., & Eichler, H.-G. (2015). The Innovative Medicines Initiative: an engine for regulatory science. *Nature Reviews. Drug Discovery*, *14*(1), 1–2. https://doi.org/10.1038/nrd4520

Goldstein, J. M., Goodman, J. M., Seidman, L. J., Kennedy, D. N., Makris, N., Lee, H., … Tsuang, M. T. (1999). Cortical abnormalities in schizophrenia identified by structural magnetic resonance imaging. *Archives of General Psychiatry*, *56*(6), 537–547.

Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N., Friston, K. J., & Frackowiak, R. S. (2001). A voxel-based morphometric study of ageing in 465 normal adult human brains. *NeuroImage*, *14*(1 Pt 1), 21–36. https://doi.org/10.1006/nimg.2001.0786

Gordon, C., & Martin, D. J. (2013). Mild cognitive impairment. *Expert Review of Neurotherapeutics*, *13*(11), 1247–1261. https://doi.org/10.1586/14737175.2013.856265

Gouw, A. A., Seewann, A., van der Flier, W. M., Barkhof, F., Rozemuller, A. M., Scheltens, P., & Geurts, J. J. G. (2011). Heterogeneity of small vessel disease: a systematic review of MRI and histopathology correlations. *Journal of Neurology, Neurosurgery, and Psychiatry*, *82*(2), 126–135. https://doi.org/10.1136/jnnp.2009.204685

Gouw, A. A., Seewann, A., Vrenken, H., van der Flier, W. M., Rozemuller, J. M., Barkhof, F., … Geurts, J. J. G. (2008). Heterogeneity of white matter hyperintensities in Alzheimer's disease: post-mortem quantitative MRI and neuropathology. *Brain: A Journal of Neurology*, *131*(Pt 12), 3286–3298. https://doi.org/10.1093/brain/awn265

Graber, M. L., Franklin, N., & Gordon, R. (2005). Diagnostic error in internal medicine. *Archives of Internal Medicine*, *165*(13), 1493–1499. https://doi.org/10.1001/archinte.165.13.1493

Greenough, A., & Graham, H. (2004). Protecting and using patient information: the role of the Caldicott Guardian. *Clinical Medicine*, *4*(3), 246–249. https://doi.org/10.7861/clinmedicine.4-3-246

Greicius, M. D., Srivastava, G., Reiss, A. L., & Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(13), 4637–4642.

Grundman, M., Pontecorvo, M. J., Salloway, S. P., Doraiswamy, P. M., Fleisher, A. S., Sadowsky, C. H., … 45-A17 Study Group. (2013). Potential impact of amyloid imaging on diagnosis and intended management in patients with progressive cognitive decline. *Alzheimer Disease and Associated Disorders*, *27*(1), 4–15. https://doi.org/10.1097/WAD.0b013e318279d02a

Gur, R. C., Turetsky, B. I., Matsui, M., Yan, M., Bilker, W., Hughett, P., & Gur, R. E. (1999). Sex Differences in Brain Gray and White Matter in Healthy Young Adults: Correlations with Cognitive Performance. *Journal of Neuroscience*, *19*(10), 4065–4072.

Hachinski, V. C., & Bowler, J. V. (1993). Vascular dementia. *Neurology*, *43*(10), 2159-2160-2161.

Haglund, M., & Englund, E. (2002). Cerebral amyloid angiopathy, white matter lesions and Alzheimer encephalopathy - a histopathological assessment. *Dementia and Geriatric Cognitive Disorders*, *14*(3), 161–166. https://doi.org/63606

Hampel, H., Blennow, K., Shaw, L. M., Hoessler, Y. C., Zetterberg, H., & Trojanowski, J. Q. (2010). Total and phosphorylated tau protein as biological markers of Alzheimer's disease. *Experimental Gerontology*, *45*(1), 30–40. https://doi.org/10.1016/j.exger.2009.10.010

Hampel, H., Buerger, K., Zinkowski, R., Teipel, S. J., Goernitz, A., Andreasen, N., … Blennow, K. (2004). Measurement of Phosphorylated Tau Epitopes in the Differential Diagnosisof Alzheimer Disease: A Comparative Cerebrospinal Fluid Study. *Archives of General Psychiatry*, *61*(1), 95–102. https://doi.org/10.1001/archpsyc.61.1.95

Hampel, H., Bürger, K., Pruessner, J. C., Zinkowski, R., DeBernardis, J., Kerkman, D., … Teipel, S. J. (2005). Correlation of Cerebrospinal Fluid Levels of Tau Protein Phosphorylated at Threonine 231 With Rates of Hippocampal Atrophy in Alzheimer Disease. *Archives of Neurology*, *62*(5), 770–773. https://doi.org/10.1001/archneur.62.5.770

Hampel, H., Frank, R., Broich, K., Teipel, S. J., Katz, R. G., Hardy, J., … Blennow, K. (2010). Biomarkers for Alzheimer's disease: academic, industry and regulatory perspectives. *Nature Reviews Drug Discovery*, *9*(7), 560–574. https://doi.org/10.1038/nrd3115

Hampel, H., Lista, S., & Khachaturian, Z. S. (2012). Development of biomarkers to chart all Alzheimer's disease stages: the royal road to cutting the therapeutic Gordian Knot. *Alzheimer's & Dementia:*

The Journal of the Alzheimer's Association, *8*(4), 312–336. https://doi.org/10.1016/j.jalz.2012.05.2116

Hanley, J. A., & McNeil, B. J. (1983). A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology*, *148*(3), 839–843. https://doi.org/10.1148/radiology.148.3.6878708

Hansson, O., Zetterberg, H., Buchhave, P., Andreasson, U., Londos, E., Minthon, L., & Blennow, K. (2007). Prediction of Alzheimer's disease using the CSF Abeta42/Abeta40 ratio in patients with mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders*, *23*(5), 316–320. https://doi.org/10.1159/000100926

Harper, L., Barkhof, F., Scheltens, P., Schott, J. M., & Fox, N. C. (2014). An algorithmic approach to structural imaging in dementia. *Journal of Neurology, Neurosurgery, and Psychiatry*, *85*(6), 692–698. https://doi.org/10.1136/jnnp-2013-306285

He, Y., Wang, L., Zang, Y., Tian, L., Zhang, X., Li, K., & Jiang, T. (2007). Regional coherence changes in the early stages of Alzheimer's disease: A combined structural and resting-state functional MRI study. *NeuroImage*, *35*(2), 488–500. https://doi.org/10.1016/j.neuroimage.2006.11.042

Herholz, K. (2012). Use of FDG PET as an imaging biomarker in clinical trials of Alzheimer's disease. *Biomarkers in Medicine*, *6*(4), 431–439. https://doi.org/10.2217/bmm.12.51

Herholz, K., Boecker, H., Nemeth, I., & Dunn, G. (2013). FDG PET in dementia multicenter studies and clinical trials. *Clinical and Translational Imaging*, *1*(4), 261–270. https://doi.org/10.1007/s40336-013-0018-y

Hesse, C., Rosengren, L., Andreasen, N., Davidsson, P., Vanderstichele, H., Vanmechelen, E., & Blennow, K. (2001). Transient increase in total tau but not phospho-tau in human cerebrospinal fluid after acute stroke. *Neuroscience Letters*, *297*(3), 187–190.

Hirono, N., Hashimoto, M., Ishii, K., Kazui, H., & Mori, E. (2004). One-year change in cerebral glucose metabolism in patients with Alzheimer's disease. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *16*(4), 488–492. https://doi.org/10.1176/jnp.16.4.488

Hodge, S., & Hailey, E. (2015, December). Second English National Memory Clinics Audit Report. Retrieved May 31, 2017, from https://www.rcpsych.ac.uk/pdf/English%20National%20Memory%20Clinics%20Audit%20Report%202014.pdf

Hort, J., Bartos, A., Pirttilä, T., & Scheltens, P. (2010). Use of cerebrospinal fluid biomarkers in diagnosis of dementia across Europe. *European Journal of Neurology*, *17*(1), 90–96. https://doi.org/10.1111/j.1468-1331.2009.02753.x

Hsieh, S., Schubert, S., Hoon, C., Mioshi, E., & Hodges, J. R. (2013). Validation of the Addenbrooke's Cognitive Examination III in frontotemporal dementia and Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *36*(3–4), 242–250. https://doi.org/10.1159/000351671

Hu, W. T., Wang, Z., Lee, V. M.-Y., Trojanowski, J. Q., Detre, J. A., & Grossman, M. (2010). Distinct cerebral perfusion patterns in FTLD and AD. *Neurology*, *75*(10), 881–888. https://doi.org/10.1212/WNL.0b013e3181f11e35

Hulley, S. B., Cummings, S. R., Browner, W. S., Grady, D. G., & Newman, T. B. (2013). *Designing Clinical Research*. Lippincott Williams & Wilkins.

Hunt, A. L., Orrison, W. W., Yeo, R. A., Haaland, K. Y., Rhyne, R. L., Garry, P. J., & Rosenberg, G. A. (1989). Clinical significance of MRI white matter lesions in the elderly. *Neurology*, *39*(11), 1470–1474.

Hunter, A. J. (2008). The Innovative Medicines Initiative: a pre-competitive initiative to enhance the biomedical science base of Europe to expedite the development of new medicines for patients. *Drug Discovery Today*, *13*(9–10), 371–373. https://doi.org/10.1016/j.drudis.2008.02.009

Ince, P. G., Minett, T., Forster, G., Brayne, C., Wharton, S. B., & Medical Research Council Cognitive Function and Ageing Neuropathology Study. (2017). Microinfarcts in an older population-representative brain donor cohort (MRC CFAS): Prevalence, relation to dementia and mobility, and implications for the evaluation of cerebral Small Vessel Disease. *Neuropathology and Applied Neurobiology*, *43*(5), 409–418. https://doi.org/10.1111/nan.12363

Institute of Medicine (US) Committee on Quality of Health Care in America. (2001). *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington (DC): National Academies Press (US). Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK222274/

Iorio, M., Spalletta, G., Chiapponi, C., Luccichenti, G., Cacciari, C., Orfei, M. D., … Piras, F. (2013). White matter hyperintensities segmentation: a new semi-automated method. *Frontiers in Aging Neuroscience*, *5*. https://doi.org/10.3389/fnagi.2013.00076

Iwashita, T. (1997). Asymptotic null and nonnull distribution of Hotelling's T2-statistic under the elliptical distribution. *Journal of Statistical Planning and Inference*, *61*(1), 85–104. https://doi.org/10.1016/S0378-3758(96)00153-X

IXICO plc. (2015). Confident and Accurate Dementia Diagnosis with Assessa®.

Jack, C. R., Barnes, J., Bernstein, M. A., Borowski, B. J., Brewer, J., Clegg, S., … Weiner, M. (2015). Magnetic Resonance Imaging in ADNI. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*, *11*(7), 740–756. https://doi.org/10.1016/j.jalz.2015.05.002

Jack, C. R., Bennett, D. A., Blennow, K., Carrillo, M. C., Feldman, H. H., Frisoni, G. B., … Dubois, B. (2016). A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers. *Neurology*, *87*(5), 539–547. https://doi.org/10.1212/WNL.0000000000002923

Jack, C. R., Bernstein, M. A., Fox, N. C., Thompson, P., Alexander, G., Harvey, D., … Weiner, M. W. (2008). The Alzheimer's disease neuroimaging initiative (ADNI): MRI methods. *Journal of Magnetic Resonance Imaging*, *27*(4), 685–691. https://doi.org/10.1002/jmri.21049

Jack, C. R., Dickson, D. W., Parisi, J. E., Xu, Y. C., Cha, R. H., O'Brien, P. C., … Petersen, R. C. (2002). Antemortem MRI Findings Correlate with Hippocampal Neuropathology in Typical Aging and Dementia. *Neurology*, *58*(5), 750–757.

Jack, C. R., Lowe, V. J., Senjem, M. L., Weigand, S. D., Kemp, B. J., Shiung, M. M., … Petersen, R. C. (2008). 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnestic mild cognitive impairment. *Brain: A Journal of Neurology*, *131*(Pt 3), 665–680. https://doi.org/10.1093/brain/awm336

Jack, C. R., Petersen, R. C., Xu, Y. C., O'Brien, P. C., Smith, G. E., Ivnik, R. J., … Kokmen, E. (1999). Prediction of AD with MRI-Based Hippocampal Volume in Mild Cognitive Impairment. *Neurology*, *52*(7), 1397–1403.

Jack, C. R., Shiung, M. M., Weigand, S. D., O'Brien, P. C., Gunter, J. L., Boeve, B. F., … Petersen, R. C. (2005). Brain atrophy rates predict subsequent clinical conversion in normal elderly and amnestic MCI. *Neurology*, *65*(8), 1227–1231. https://doi.org/10.1212/01.wnl.0000180958.22678.91

Jack, C. R., Twomey, C. K., Zinsmeister, A. R., Sharbrough, F. W., Petersen, R. C., & Cascino, G. D. (1989). Anterior temporal lobes and hippocampal formations: normative volumetric measurements from MR images in young adults. *Radiology*, *172*(2), 549–554. https://doi.org/10.1148/radiology.172.2.2748838

Jack Jr., C. R., Albert, M. S., Knopman, D. S., McKhann, G. M., Sperling, R. A., Carrillo, M. C., … Phelps, C. H. (2011). Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, *7*(3), 257–262. https://doi.org/10.1016/j.jalz.2011.03.004

Jack Jr, C. R., Knopman, D. S., Jagust, W. J., Shaw, L. M., Aisen, P. S., Weiner, M. W., … Trojanowski, J. Q. (2010). Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *The Lancet Neurology*, *9*(1), 119–128. https://doi.org/10.1016/S1474-4422(09)70299-6

Jagust, W., Reed, B., Mungas, D., Ellis, W., & Decarli, C. (2007). What does fluorodeoxyglucose PET imaging add to a clinical diagnosis of dementia? *Neurology*, *69*(9), 871–877. https://doi.org/10.1212/01.wnl.0000269790.05105.16

Janoutová, J., Šerý, O., Hosák, L., & Janout, V. (2015). Is Mild Cognitive Impairment a Precursor of Alzheimer's Disease? Short Review. *Central European Journal of Public Health*, *23*(4), 365–367. https://doi.org/10.21101/cejph.a4414

Jellinger, K. A. (2008). Morphologic diagnosis of "vascular dementia" - a critical update. *Journal of the Neurological Sciences*, *270*(1–2), 1–12. https://doi.org/10.1016/j.jns.2008.03.006

Jellinger, K. A., & Attems, J. (2007). Neuropathological evaluation of mixed dementia. *Journal of the Neurological Sciences*, *257*(1–2), 80–87. https://doi.org/10.1016/j.jns.2007.01.045

Jensen, P. B., Jensen, L. J., & Brunak, S. (2012). Mining electronic health records: towards better research applications and clinical care. *Nature Reviews Genetics*, *13*(6), 395–405. https://doi.org/10.1038/nrg3208

Jicha, G. A., Parisi, J. E., Dickson, D. W., Johnson, K., Cha, R., Ivnik, R. J., … Petersen, R. C. (2006). Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia. *Archives of Neurology*, *63*(5), 674–681. https://doi.org/10.1001/archneur.63.5.674

Jindal, H., Bhatt, B., Sk, S., & Singh Malik, J. (2014). Alzheimer disease immunotherapeutics: Then and now. *Human Vaccines & Immunotherapeutics*, *10*(9), 2741–2743. https://doi.org/10.4161/21645515.2014.970959

Johnson, K. A., Fox, N. C., Sperling, R. A., & Klunk, W. E. (2012). Brain Imaging in Alzheimer Disease. *Cold Spring Harbor Perspectives in Medicine*, *2*(4), a006213. https://doi.org/10.1101/cshperspect.a006213

Johnson, K. A., Schultz, A., Betensky, R. A., Becker, J. A., Sepulcre, J., Rentz, D., … Sperling, R. (2016). Tau positron emission tomographic imaging in aging and early Alzheimer disease. *Annals of Neurology*, *79*(1), 110–119. https://doi.org/10.1002/ana.24546

Kantarci, K. (2007). 1H magnetic resonance spectroscopy in dementia. *The British Journal of Radiology*, *80 Spec No 2*, S146-152. https://doi.org/10.1259/bjr/60346217

Kapasi, A., DeCarli, C., & Schneider, J. A. (2017). Impact of multiple pathologies on the threshold for clinically overt dementia. *Acta Neuropathologica*, *134*(2), 171–186. https://doi.org/10.1007/s00401-017-1717-7

Karran, E., Mercken, M., & Strooper, B. D. (2011). The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. *Nature Reviews Drug Discovery*, *10*(9), 698–712. https://doi.org/10.1038/nrd3505

Kennedy, A. M., Frackowiak, R. S. J., Newman, S. K., Bloomfield, P. M., Seaward, J., Roques, P., … Rossor, M. N. (1995). Deficits in cerebral glucose metabolism demonstrated by positron emission tomography in individuals at risk of familial Alzheimer's disease. *Neuroscience Letters*, *186*(1), 17–20. https://doi.org/10.1016/0304-3940(95)11270-7

Khan, W., Westman, E., Jones, N., Wahlund, L.-O., Mecocci, P., Vellas, B., … Simmons, A. (2015). Automated Hippocampal Subfield Measures as Predictors of Conversion from Mild Cognitive Impairment to Alzheimer's Disease in Two Independent Cohorts. *Brain Topography*, *28*(5), 746–759. https://doi.org/10.1007/s10548-014-0415-1

Kim, G. H., Lee, J. H., Seo, S. W., Kim, J. H., Seong, J.-K., Ye, B. S., … Na, D. L. (2015). Hippocampal volume and shape in pure subcortical vascular dementia. *Neurobiology of Aging*, *36*(1), 485–491. https://doi.org/10.1016/j.neurobiolaging.2014.08.009

Klöppel, S., Stonnington, C. M., Barnes, J., Chen, F., Chu, C., Good, C. D., … Frackowiak, R. S. J. (2008). Accuracy of dementia diagnosis—a direct comparison between radiologists and a computerized method. *Brain*, *131*(11), 2969–2974. https://doi.org/10.1093/brain/awn239

Klunk, W. E., Engler, H., Nordberg, A., Wang, Y., Blomqvist, G., Holt, D. P., … Långström, B. (2004). Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Annals of Neurology*, *55*(3), 306–319. https://doi.org/10.1002/ana.20009

Knopman, D. S., Parisi, J. E., Salviati, A., Floriach-Robert, M., Boeve, B. F., Ivnik, R. J., … Petersen, R. C. (2003). Neuropathology of Cognitively Normal Elderly. *Journal of Neuropathology & Experimental Neurology*, *62*(11), 1087–1095. https://doi.org/10.1093/jnen/62.11.1087

Koedam, E. L. G. E., Lauffer, V., van der Vlies, A. E., van der Flier, W. M., Scheltens, P., & Pijnenburg, Y. A. L. (2010). Early-versus late-onset Alzheimer's disease: more than age alone. *Journal of Alzheimer's Disease: JAD*, *19*(4), 1401–1408. https://doi.org/10.3233/JAD-2010-1337

Koedam, E. L. G. E., Lehmann, M., Flier, W. M., Scheltens, P., Pijnenburg, Y. A. L., Fox, N., … Wattjes, M. P. (2011). Visual assessment of posterior atrophy development of a MRI rating scale. *European Radiology*, *21*(12), 2618–2625. https://doi.org/10.1007/s00330-011-2205-4

Korczyn, A. D. (2002). Mixed dementia--the most common cause of dementia. *Annals of the New York Academy of Sciences*, *977*, 129–134.

Kudo, Y., Okamura, N., Furumoto, S., Tashiro, M., Furukawa, K., Maruyama, M., … Arai, H. (2007). 2-(2-[2-Dimethylaminothiazol-5-yl]ethenyl)-6- (2-[fluoro]ethoxy)benzoxazole: a novel PET agent for in vivo detection of dense amyloid plaques in Alzheimer's disease patients. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine*, *48*(4), 553–561.

Lace, G., Savva, G. M., Forster, G., de Silva, R., Brayne, C., Matthews, F. E., … Wharton, S. B. (2009). Hippocampal tau pathology is related to neuroanatomical connections: an ageing population-based study. *Brain*, *132*(5), 1324–1334. https://doi.org/10.1093/brain/awp059

Lam, B., Masellis, M., Freedman, M., Stuss, D. T., & Black, S. E. (2013). Clinical, imaging, and pathological heterogeneity of the Alzheimer's disease syndrome. *Alzheimer's Research & Therapy*, *5*(1), 1. https://doi.org/10.1186/alzrt155

Landau, S. M., Harvey, D., Madison, C. M., Koeppe, R. A., Reiman, E. M., Foster, N. L., … Alzheimer's Disease Neuroimaging Initiative. (2011). Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI. *Neurobiology of Aging*, *32*(7), 1207–1218. https://doi.org/10.1016/j.neurobiolaging.2009.07.002

Larner, A. J., & Mitchell, A. J. (2014). A meta-analysis of the accuracy of the Addenbrooke's Cognitive Examination (ACE) and the Addenbrooke's Cognitive Examination-Revised (ACE-R) in the detection of dementia. *International Psychogeriatrics*, *26*(4), 555–563. https://doi.org/10.1017/S1041610213002329

Launer, L. J., Hughes, T. M., & White, L. R. (2011). Microinfarcts, brain atrophy, and cognitive function: the Honolulu Asia Aging Study Autopsy Study. *Annals of Neurology*, *70*(5), 774–780. https://doi.org/10.1002/ana.22520

Launer, L. J., Wind, A. W., & Deeg, D. J. (1994). Nonresponse pattern and bias in a community-based cross-sectional study of cognitive functioning among the elderly. *American Journal of Epidemiology*, *139*(8), 803–812.

Lee, E. C., Whitehead, A. L., Jacques, R. M., & Julious, S. A. (2014). The statistical interpretation of pilot trials: should significance thresholds be reconsidered? *BMC Medical Research Methodology*, *14*, 41. https://doi.org/10.1186/1471-2288-14-41

Lehmann, M., Koedam, E. L. G. E., Barnes, J., Bartlett, J. W., Ryan, N. S., Pijnenburg, Y. A. L., … Fox, N. C. (2012). Posterior cerebral atrophy in the absence of medial temporal lobe atrophy in pathologically-confirmed Alzheimer's disease. *Neurobiology of Aging*, *33*(3), 627.e1-627.e12. https://doi.org/10.1016/j.neurobiolaging.2011.04.003

Levine, B., Kovacevic, N., Nica, E. I., Cheung, G., Gao, F., Schwartz, M. L., & Black, S. E. (2008). The Toronto traumatic brain injury study Injury severity and quantified MRI. *Neurology*, *70*(10), 771–778. https://doi.org/10.1212/01.wnl.0000304108.32283.aa

Li, J.-Q., Tan, L., Wang, H.-F., Tan, M.-S., Tan, L., Xu, W., … Yu, J.-T. (2016). Risk factors for predicting progression from mild cognitive impairment to Alzheimer's disease: a systematic review and meta-analysis of cohort studies. *Journal of Neurology, Neurosurgery, and Psychiatry*, *87*(5), 476–484. https://doi.org/10.1136/jnnp-2014-310095

Liu, Y., Paajanen, T., Westman, E., Wahlund, L.-O., Simmons, A., Tunnard, C., … Soininen for the AddNeuroMed Consortium, H. (2010). Effect of APOE ε4 Allele on Cortical Thicknesses and Volumes: The AddNeuroMed Study. *Journal of Alzheimer's Disease*, *21*(3), 947–966. https://doi.org/10.3233/JAD-2010-100201

Liu, Y., Paajanen, T., Westman, E., Zhang, Y., Wahlund, L.-O., Simmons, A., … AddNeuroMed Consortium. (2010). APOE ε2 allele is associated with larger regional cortical thicknesses and volumes. *Dementia and Geriatric Cognitive Disorders*, *30*(3), 229–237. https://doi.org/10.1159/000320136

Liu, Y., Paajanen, T., Zhang, Y., Westman, E., Wahlund, L.-O., Simmons, A., … AddNeuroMed Consortium. (2010). Analysis of regional MRI volumes and thicknesses as predictors of conversion from mild cognitive impairment to Alzheimer's disease. *Neurobiology of Aging*, *31*(8), 1375–1385. https://doi.org/10.1016/j.neurobiolaging.2010.01.022

Liu, Y., Paajanen, T., Zhang, Y., Westman, E., Wahlund, L.-O., Simmons, A., … AddNeuroMed Consortium. (2011). Combination analysis of neuropsychological tests and structural MRI measures in

differentiating AD, MCI and control groups--the AddNeuroMed study. *Neurobiology of Aging*, *32*(7), 1198–1206. https://doi.org/10.1016/j.neurobiolaging.2009.07.008

Liu, Y., Wang, K., Yu, C., He, Y., Zhou, Y., Liang, M., … Jiang, T. (2008). Regional homogeneity, functional connectivity and imaging markers of Alzheimer's disease: A review of resting-state fMRI studies. *Neuropsychologia*, *46*(6), 1648–1656. https://doi.org/10.1016/j.neuropsychologia.2008.01.027

Livingston, G., Sommerlad, A., Orgeta, V., Costafreda, S. G., Huntley, J., Ames, D., … Mukadam, N. (2017). Dementia prevention, intervention, and care. *The Lancet*, *390*(10113), 2673–2734. https://doi.org/10.1016/S0140-6736(17)31363-6

Lliffe, S., & Manthorpe, J. (2004). The hazards of early recognition of dementia: a risk assessment. *Aging & Mental Health*, *8*(2), 99–105. https://doi.org/10.1080/13607860410001649653

Lovestone, S., Francis, P., Kloszewska, I., Mecocci, P., Simmons, A., Soininen, H., … on behalf of the AddNeuroMed Consortium. (2009). AddNeuroMed—The European Collaboration for the Discovery of Novel Biomarkers for Alzheimer's Disease. *Annals of the New York Academy of Sciences*, *1180*(1), 36–46. https://doi.org/10.1111/j.1749-6632.2009.05064.x

Mahley, R. W., & Rall, S. C. (2000). APOLIPOPROTEIN E: Far More Than a Lipid Transport Protein. *Annual Review of Genomics and Human Genetics*, *1*(1), 507–537. https://doi.org/10.1146/annurev.genom.1.1.507

Maillard, P., Carmichael, O., Fletcher, E., Reed, B., Mungas, D., & DeCarli, C. (2012). Coevolution of white matter hyperintensities and cognition in the elderly. *Neurology*, *79*(5), 442–448. https://doi.org/10.1212/WNL.0b013e3182617136

Malin, B., Benitez, K., & Masys, D. (2011). Never too old for anonymity: a statistical standard for demographic data sharing via the HIPAA Privacy Rule. *Journal of the American Medical Informatics Association : JAMIA*, *18*(1), 3–10. https://doi.org/10.1136/jamia.2010.004622

Maller, J. J., Réglade-Meslin, C., Anstey, K. J., & Sachdev, P. (2006). Sex and symmetry differences in hippocampal volumetrics: Before and beyond the opening of the crus of the fornix. *Hippocampus*, *16*(1), 80–90. https://doi.org/10.1002/hipo.20133

Malone, I. B., Leung, K. K., Clegg, S., Barnes, J., Whitwell, J. L., Ashburner, J., … Ridgway, G. R. (2015). Accurate automatic estimation of total intracranial volume: a nuisance variable with less nuisance. *NeuroImage*, *104*, 366–372. https://doi.org/10.1016/j.neuroimage.2014.09.034

Mangialasche, F., Solomon, A., Winblad, B., Mecocci, P., & Kivipelto, M. (2010). Alzheimer's disease: clinical trials and drug development. *The Lancet. Neurology*, *9*(7), 702–716. https://doi.org/10.1016/S1474-4422(10)70119-8

Manning, E. N., Barnes, J., Cash, D. M., Bartlett, J. W., Leung, K. K., Ourselin, S., & Nick C. Fox1 for the Alzheimer's Disease NeuroImaging Initiative. (2014). APOE ε4 Is Associated with Disproportionate Progressive Hippocampal Atrophy in AD. *PLoS ONE*, *9*(5), e97608. https://doi.org/10.1371/journal.pone.0097608

Manolio, T. A., Kronmal, R. A., Burke, G. L., Poirier, V., O'Leary, D. H., Gardin, J. M., … Bryan, R. N. (1994). Magnetic resonance abnormalities and cardiovascular disease in older adults. The Cardiovascular Health Study. *Stroke*, *25*(2), 318–327. https://doi.org/10.1161/01.STR.25.2.318

Mäntylä, R., Erkinjuntti, T., Salonen, O., Aronen, H. J., Peltonen, T., Pohjasvaara, T., & Standertskjöld-Nordenstam, C. G. (1997). Variable agreement between visual rating scales for white matter hyperintensities on MRI. Comparison of 13 rating scales in a poststroke cohort. *Stroke*, *28*(8), 1614–1623.

Maruszak, A., & Thuret, S. (2014). Why looking at the whole hippocampus is not enough—a critical role for anteroposterior axis, subfield and activation analyses to enhance predictive value of hippocampal changes for Alzheimer's disease diagnosis. *Frontiers in Cellular Neuroscience*, *8*. https://doi.org/10.3389/fncel.2014.00095

Masters, C. L., Cappai, R., Barnham, K. J., & Villemagne, V. L. (2006). Molecular mechanisms for Alzheimer's disease: implications for neuroimaging and therapeutics. *Journal of Neurochemistry*, *97*(6), 1700–1725. https://doi.org/10.1111/j.1471-4159.2006.03989.x

Matthew McBee. (2010). Modeling Outcomes With Floor or Ceiling Effects: An Introduction to the Tobit Model. *Gifted Child Quarterly*, *54*(4), 314–320. https://doi.org/10.1177/0016986210379095

Mattsson, N., Andreasson, U., Persson, S., Arai, H., Batish, S. D., Bernardini, S., … Blennow, K. (2011). The Alzheimer's Association external quality control program for cerebrospinal fluid biomarkers. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *7*(4), 386–395.e6. https://doi.org/10.1016/j.jalz.2011.05.2243

Mattsson, N., Brax, D., & Zetterberg, H. (2010). To know or not to know: ethical issues related to early diagnosis of Alzheimer's disease. *International Journal of Alzheimer's Disease*, *2010*. https://doi.org/10.4061/2010/841941

Mattsson, N., Zetterberg, H., Hansson, O., Andreasen, N., Parnetti, L., Jonsson, M., … Blennow, K. (2009). CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. *JAMA*, *302*(4), 385–393. https://doi.org/10.1001/jama.2009.1064

Mawuenyega, K. G., Sigurdson, W., Ovod, V., Munsell, L., Kasten, T., Morris, J. C., … Bateman, R. J. (2010). Decreased clearance of CNS beta-amyloid in Alzheimer's disease. *Science (New York, N.Y.)*, *330*(6012), 1774. https://doi.org/10.1126/science.1197623

McDonald, C. R., Gharapetian, L., McEvoy, L. K., Fennema-Notestine, C., Hagler, D. J., Holland, D., … Alzheimer's Disease Neuroimaging Initiative. (2012). Relationship between regional atrophy rates and cognitive decline in mild cognitive impairment. *Neurobiology of Aging*, *33*(2), 242–253. https://doi.org/10.1016/j.neurobiolaging.2010.03.015

McIntosh, A. R., & Lobaugh, N. J. (2004). Partial least squares analysis of neuroimaging data: applications and advances. *NeuroImage*, *23*, S250–S263. https://doi.org/10.1016/j.neuroimage.2004.07.020

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, *34*(7), 939–939. https://doi.org/10.1212/WNL.34.7.939

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Kawas, C. H., … Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *7*(3), 263–269. https://doi.org/10.1016/j.jalz.2011.03.005

Menachemi, N., & Collum, T. H. (2011). Benefits and drawbacks of electronic health record systems. *Risk Management and Healthcare Policy*, *4*, 47–55. https://doi.org/10.2147/RMHP.S12985

Menachemi, N., Powers, T. L., & Brooks, R. G. (2009). The role of information technology usage in physician practice satisfaction. *Health Care Management Review*, *34*(4), 364–371. https://doi.org/10.1097/HMR.0b013e3181a90d53

Mendez, M. F. (2017). Early-Onset Alzheimer Disease. *Neurologic Clinics*, *35*(2), 263–281. https://doi.org/10.1016/j.ncl.2017.01.005

Meng, X., & D'Arcy, C. (2012). Education and dementia in the context of the cognitive reserve hypothesis: a systematic review with meta-analyses and qualitative analyses. *PloS One*, *7*(6), e38268. https://doi.org/10.1371/journal.pone.0038268

Metz, C. E. (2006). Receiver Operating Characteristic Analysis: A Tool for the Quantitative Evaluation of Observer Performance and Imaging Systems. *Journal of the American College of Radiology*, *3*(6), 413–422. https://doi.org/10.1016/j.jacr.2006.02.021

Meystre, S. M., Friedlin, F. J., South, B. R., Shen, S., & Samore, M. H. (2010). Automatic de-identification of textual documents in the electronic health record: a review of recent research. *BMC Medical Research Methodology*, *10*, 70. https://doi.org/10.1186/1471-2288-10-70

Milne, A. (2010). Dementia screening and early diagnosis: The case for and against. *Health, Risk & Society*, *12*(1), 65–76. https://doi.org/10.1080/13698570903509497

Mintun, M. A., Larossa, G. N., Sheline, Y. I., Dence, C. S., Lee, S. Y., Mach, R. H., … Morris, J. C. (2006). [11C]PIB in a nondemented population: potential antecedent marker of Alzheimer disease. *Neurology*, *67*(3), 446–452. https://doi.org/10.1212/01.wnl.0000228230.26044.a4

Mistry, H., & Sauer, J. (2009). Psychiatrists and electronic patient records: the South London and Maudsley experience. *The Psychiatrist*, *33*(9), 325–328. https://doi.org/10.1192/pb.bp.108.019588

Mitchell, A. J. (2009). A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. *Journal of Psychiatric Research*, *43*(4), 411–431. https://doi.org/10.1016/j.jpsychires.2008.04.014

Moody, D. M., Brown, W. R., Challa, V. R., & Anderson, R. L. (1995). Periventricular venous collagenosis: association with leukoaraiosis. *Radiology*, *194*(2), 469–476. https://doi.org/10.1148/radiology.194.2.7824728

Morris, J. C., & Price, J. L. (2001). Pathologic correlates of nondemented aging, mild cognitive impairment, and early-stage Alzheimer's disease. *Journal of Molecular Neuroscience: MN*, *17*(2), 101–118.

Morris, J. C., Roe, C. M., Grant, E. A., Head, D., Storandt, M., Goate, A. M., … Mintun, M. A. (2009). Pittsburgh compound B imaging and prediction of progression from cognitive normality to symptomatic Alzheimer disease. *Archives of Neurology*, *66*(12), 1469–1475. https://doi.org/10.1001/archneurol.2009.269

Morrison, Z., Robertson, A., Cresswell, K., Crowe, S., & Sheikh, A. (2011). Understanding Contrasting Approaches to Nationwide Implementations of Electronic Health Record Systems: England, the USA and Australia. *Journal of Healthcare Engineering*, *2*(1), 25–41. https://doi.org/10.1260/2040-2295.2.1.25

Mortamais, M., Portet, F., Brickman, A. M., Provenzano, F. A., Muraskin, J., Akbaraly, T. N., … Artero, S. (2014). Education modulates the impact of white matter lesions on the risk of mild cognitive impairment and dementia. *The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry*, *22*(11), 1336–1345. https://doi.org/10.1016/j.jagp.2013.06.002

Mosconi, L., De Santi, S., Li, Y., Li, J., Zhan, J., Tsui, W. H., … de Leon, M. J. (2006). Visual rating of medial temporal lobe metabolism in mild cognitive impairment and Alzheimer's disease using FDG-PET. *European Journal of Nuclear Medicine and Molecular Imaging*, *33*(2), 210–221. https://doi.org/10.1007/s00259-005-1956-z

Mosconi, L., Nacmias, B., Sorbi, S., Cristofaro, M. T. R. D., Fayazz, M., Tedde, A., … Pupi, A. (2004). Brain metabolic decreases related to the dose of the ApoE e4 allele in Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *75*(3), 370–376. https://doi.org/10.1136/jnnp.2003.014993

Mueller, S. G., Weiner, M. W., Thal, L. J., Petersen, R. C., Jack, C., Jagust, W., … Beckett, L. (2005). The Alzheimer's Disease Neuroimaging Initiative. *Neuroimaging Clinics of North America*, *15*(4), 869–xii. https://doi.org/10.1016/j.nic.2005.09.008

Mungas, D., Reed, B. R., Jagust, W. J., DeCarli, C., Mack, W. J., Kramer, J. H., … Chui, H. C. (2002). Volumetric MRI predicts rate of cognitive decline related to AD and cerebrovascular disease. *Neurology*, *59*(6), 867–873.

National Collaborating Centre for Mental Health. (2007). *Dementia: the NICE-SCIE guideline on supporting people with dementia and their carers in health and social care.* (NICE Practice Guidelines No. Technical Report 42). Retrieved from https://www.nice.org.uk/guidance/cg42

Neamatullah, I., Douglass, M. M., Lehman, L. H., Reisner, A., Villarroel, M., Long, W. J., … Clifford, G. D. (2008). Automated de-identification of free-text medical records. *BMC Medical Informatics and Decision Making*, *8*, 32. https://doi.org/10.1186/1472-6947-8-32

Nelissen, N., Van Laere, K., Thurfjell, L., Owenius, R., Vandenbulcke, M., Koole, M., … Vandenberghe, R. (2009). Phase 1 study of the Pittsburgh compound B derivative 18F-flutemetamol in healthy volunteers and patients with probable Alzheimer disease. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine*, *50*(8), 1251–1259. https://doi.org/10.2967/jnumed.109.063305

Newgard, C. D., Zive, D., Jui, J., Weathers, C., & Daya, M. (2012). Electronic Versus Manual Data Processing: Evaluating the Use of Electronic Health Records in Out-of-hospital Clinical Research. *Academic Emergency Medicine*, *19*(2), 217–227. https://doi.org/10.1111/j.1553-2712.2011.01275.x

Niemantsverdriet, E., Feyen, B. F. E., Le Bastard, N., Martin, J.-J., Goeman, J., De Deyn, P. P., & Engelborghs, S. (2015). Overdiagnosing Vascular Dementia using Structural Brain Imaging for Dementia Work-Up. *Journal of Alzheimer's Disease: JAD*, *45*(4), 1039–1043. https://doi.org/10.3233/JAD-142103

Nir, T. M., Villalon-Reina, J. E., Prasad, G., Jahanshad, N., Joshi, S. H., Toga, A. W., … Thompson, P. M. (2015). Diffusion weighted imaging-based maximum density path analysis and classification of Alzheimer's disease. *Neurobiology of Aging*, *36*, *Supplement 1*, S132–S140. https://doi.org/10.1016/j.neurobiolaging.2014.05.037

Noh, Y., Jeon, S., Lee, J. M., Seo, S. W., Kim, G. H., Cho, H., … Na, D. L. (2014). Anatomical heterogeneity of Alzheimer disease: based on cortical thickness on MRIs. *Neurology*, *83*(21), 1936–1944. https://doi.org/10.1212/WNL.0000000000001003

Nordenskjöld, R., Malmberg, F., Larsson, E.-M., Simmons, A., Ahlström, H., Johansson, L., & Kullberg, J. (2015). Intracranial volume normalization methods: Considerations when investigating gender differences in regional brain volume. *Psychiatry Research: Neuroimaging*, *231*(3), 227–235. https://doi.org/10.1016/j.pscychresns.2014.11.011

Nordenskjöld, R., Malmberg, F., Larsson, E.-M., Simmons, A., Brooks, S. J., Lind, L., … Kullberg, J. (2013). Intracranial volume estimated with commonly used methods could introduce bias in studies including brain volume measurements. *NeuroImage*, *83*, 355–360. https://doi.org/10.1016/j.neuroimage.2013.06.068

Nyberg, L. (2017). Functional brain imaging of episodic memory decline in ageing. *Journal of Internal Medicine*, *281*(1), 65–74. https://doi.org/10.1111/joim.12533

O'Brien, J. T., Erkinjuntti, T., Reisberg, B., Roman, G., Sawada, T., Pantoni, L., … DeKosky, S. T. (2003). Vascular cognitive impairment. *The Lancet. Neurology*, *2*(2), 89–98.

O'Brien, J. T., & Thomas, A. (2015a). Vascular dementia. *The Lancet*, *386*(10004), 1698–1706. https://doi.org/10.1016/S0140-6736(15)00463-8

O'Brien, J. T., & Thomas, A. (2015b). Vascular dementia. *The Lancet*, *386*(10004), 1698–1706. https://doi.org/10.1016/S0140-6736(15)00463-8

O'Brien, L. M., Ziegler, D. A., Deutsch, C. K., Frazier, J. A., Herbert, M. R., & Locascio, J. J. (2011). Statistical adjustments for brain size in volumetric neuroimaging studies: Some practical implications in methods. *Psychiatry Research*, *193*(2), 113–122. https://doi.org/10.1016/j.pscychresns.2011.01.007

Oppedal, K., Aarsland, D., Firbank, M. J., Sonnesyn, H., Tysnes, O. B., O'Brien, J. T., & Beyer, M. K. (2012). White Matter Hyperintensities in Mild Lewy Body Dementia. *Dementia and Geriatric Cognitive Disorders EXTRA*, *2*(1), 481–495. https://doi.org/10.1159/000343480

Ost, M., Nylén, K., Csajbok, L., Ohrfelt, A. O., Tullberg, M., Wikkelsö, C., … Nellgård, B. (2006). Initial CSF total tau correlates with 1-year outcome in patients with traumatic brain injury. *Neurology*, *67*(9), 1600–1604. https://doi.org/10.1212/01.wnl.0000242732.06714.0f

O'Sullivan, M., Jouvent, E., Saemann, P. G., Mangin, J.-F., Viswanathan, A., Gschwendtner, A., … Dichgans, M. (2008). Measurement of brain atrophy in subcortical vascular disease: a comparison of different approaches and the impact of ischaemic lesions. *NeuroImage*, *43*(2), 312–320. https://doi.org/10.1016/j.neuroimage.2008.07.049

Pantoni, L. (2010). Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *The Lancet Neurology*, *9*(7), 689–701. https://doi.org/10.1016/S1474-4422(10)70104-6

Pasquier, F., Leys, D., Weerts, J. G. E., Mourner-Vehier, F., Barkhof, F., & Scheltens, P. (1996). Inter-and Intraobserver Reproducibility of Cerebral Atrophy Assessment on MRI Scans with Hemispheric Infarcts. *European Neurology*, *36*(5), 268–272. https://doi.org/10.1159/000117270

Pedraza, O., Bowers, D., & Gilmore, R. (2004). Asymmetry of the hippocampus and amygdala in MRI volumetric measurements of normal adults. *Journal of the International Neuropsychological Society*, *10*(5), 664–678. https://doi.org/10.1017/S1355617704105080

Peng, G.-P., Feng, Z., He, F.-P., Chen, Z.-Q., Liu, X.-Y., Liu, P., & Luo, B.-Y. (2015). Correlation of Hippocampal Volume and Cognitive Performances in Patients with Either Mild Cognitive Impairment or Alzheimer's disease. *CNS Neuroscience & Therapeutics*, *21*(1), 15–22. https://doi.org/10.1111/cns.12317

Pereira, J. B., Cavallin, L., Spulber, G., Aguilar, C., Mecocci, P., Vellas, B., … AddNeuroMed consortium and for the Alzheimer's Disease Neuroimaging Initiative. (2014a). Influence of age, disease onset and ApoE4 on visual medial temporal lobe atrophy cut-offs. *Journal of Internal Medicine*, *275*(3), 317–330. https://doi.org/10.1111/joim.12148

Pereira, J. B., Cavallin, L., Spulber, G., Aguilar, C., Mecocci, P., Vellas, B., … AddNeuroMed consortium and for the Alzheimer's Disease Neuroimaging Initiative. (2014b). Influence of age, disease onset and ApoE4 on visual medial temporal lobe atrophy cut-offs. *Journal of Internal Medicine*, *275*(3), 317–330. https://doi.org/10.1111/joim.12148

Perera, G., Broadbent, M., Callard, F., Chang, C.-K., Downs, J., Dutta, R., … Stewart, R. (2016). Cohort profile of the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) Case Register: current status and recent enhancement of an Electronic Mental Health Record-derived data resource. *BMJ Open*, *6*(3), e008721. https://doi.org/10.1136/bmjopen-2015-008721

Perry, E., Ziabreva, I., Perry, R., Aarsland, D., & Ballard, C. (2005). Absence of cholinergic deficits in "pure" vascular dementia. *Neurology*, *64*(1), 132–133. https://doi.org/10.1212/01.WNL.0000148591.63727.80

Petcharunpaisan, S., Ramalho, J., & Castillo, M. (2010). Arterial spin labeling in neuroimaging. *World Journal of Radiology*, *2*(10), 384–398. https://doi.org/10.4329/wjr.v2.i10.384

Petersen, R. C., Aisen, P. S., Beckett, L. A., Donohue, M. C., Gamst, A. C., Harvey, D. J., … Weiner, M. W. (2010). Alzheimer's Disease Neuroimaging Initiative (ADNI). *Neurology*, *74*(3), 201–209. https://doi.org/10.1212/WNL.0b013e3181cb3e25

Petersen, R. C., Parisi, J. E., Dickson, D. W., Johnson, K. A., Knopman, D. S., Boeve, B. F., … Kokmen, E. (2006). Neuropathologic features of amnestic mild cognitive impairment. *Archives of Neurology*, *63*(5), 665–672. https://doi.org/10.1001/archneur.63.5.665

Pike, K. E., Savage, G., Villemagne, V. L., Ng, S., Moss, S. A., Maruff, P., … Rowe, C. C. (2007). Beta-amyloid imaging and memory in non-demented individuals: evidence for preclinical Alzheimer's disease. *Brain: A Journal of Neurology*, *130*(Pt 11), 2837–2844. https://doi.org/10.1093/brain/awm238

Pimplikar, S. W., Nixon, R. A., Robakis, N. K., Shen, J., & Tsai, L.-H. (2010). Amyloid-Independent Mechanisms in Alzheimer's Disease Pathogenesis. *Journal of Neuroscience*, *30*(45), 14946–14954. https://doi.org/10.1523/JNEUROSCI.4305-10.2010

Pini, L., Pievani, M., Bocchetta, M., Altomare, D., Bosco, P., Cavedo, E., … Frisoni, G. B. (2016). Brain atrophy in Alzheimer's Disease and aging. *Ageing Research Reviews*, *30*, 25–48. https://doi.org/10.1016/j.arr.2016.01.002

Price, J. C., Klunk, W. E., Lopresti, B. J., Lu, X., Hoge, J. A., Ziolko, S. K., … Mathis, C. A. (2005). Kinetic modeling of amyloid binding in humans using PET imaging and Pittsburgh Compound-B. *Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, *25*(11), 1528–1547. https://doi.org/10.1038/sj.jcbfm.9600146

Price, J. L., Ko, A. I., Wade, M. J., Tsou, S. K., McKeel, D. W., & Morris, J. C. (2001). Neuron number in the entorhinal cortex and CA1 in preclinical Alzheimer disease. *Archives of Neurology*, *58*(9), 1395–1402.

Price, M., Bryce, R., & Ferri, C. P. (2011). *World Alzheimer Report 2011: The benefits of early diagnosis and intervention*. Alzheimer's Disease International (ADI). Retrieved from https://www.alz.co.uk/research/WorldAlzheimerReport2011.pdf

Prince, M., Bryce, R., Albanese, E., Wimo, A., Ribeiro, W., & Ferri, C. P. (2013). The global prevalence of dementia: A systematic review and metaanalysis. *Alzheimer's & Dementia*, *9*(1), 63–75.e2. https://doi.org/10.1016/j.jalz.2012.11.007

Qizilbash, N., Schneider, L. S., Chui, H., Tariot, P., Brodaty, H., Kaye, J., & Erkinjuntti, T. (Eds.). (2002). *Evidence-based dementia practice*. Osney Mead, Oxford, UK ; Malden, MA, USA: Blackwell Science.

Rabinovici, G. D., Furst, A. J., O'Neil, J. P., Racine, C. A., Mormino, E. C., Baker, S. L., … Jagust, W. J. (2007). 11C-PIB PET imaging in Alzheimer disease and frontotemporal lobar degeneration. *Neurology*, *68*(15), 1205–1212. https://doi.org/10.1212/01.wnl.0000259035.98480.ed

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences*, *98*(2), 676–682. https://doi.org/10.1073/pnas.98.2.676

Ramirez, J., McNeely, A. A., Scott, C. J., Stuss, D. T., & Black, S. E. (2014). Subcortical hyperintensity volumetrics in Alzheimer's disease and normal elderly in the Sunnybrook Dementia Study: correlations with atrophy, executive function, mental processing speed, and verbal memory. *Alzheimer's Research & Therapy*, *6*(4), 49. https://doi.org/10.1186/alzrt279

Reed, B. R., Mungas, D. M., Kramer, J. H., Betz, B. P., Ellis, W., Vinters, H. V., … Chui, H. C. (2004). Clinical and neuropsychological features in autopsy-defined vascular dementia. *The Clinical Neuropsychologist*, *18*(1), 63–74. https://doi.org/10.1080/13854040490507163

Ridha, D. B. H., Anderson, V. M., Barnes, J., Boyes, R. G., Price, S. L., Rossor, M. N., … Fox, N. C. (2008). Volumetric MRI and cognitive measures in Alzheimer disease. *Journal of Neurology*, *255*(4), 567–574. https://doi.org/10.1007/s00415-008-0750-9

Rockwood, K., Wentzel, C., Hachinski, V., Hogan, D. B., MacKnight, C., & McDowell, I. (2000). Prevalence and outcomes of vascular cognitive impairment. Vascular Cognitive Impairment Investigators of the Canadian Study of Health and Aging. *Neurology*, *54*(2), 447–451.

Roher, A. E., Weiss, N., Kokjohn, T. A., Kuo, Y.-M., Kalback, W., Anthony, J., … Beach, T. (2002). Increased A beta peptides and reduced cholesterol and myelin proteins characterize white matter degeneration in Alzheimer's disease. *Biochemistry*, *41*(37), 11080–11090.

Román, G. C. (2002). Vascular dementia may be the most common form of dementia in the elderly. *Journal of the Neurological Sciences*, *203–204*, 7–10.

Román, G. C., Tatemichi, T. K., Erkinjuntti, T., Cummings, J. L., Masdeu, J. C., Garcia, J. H., … Scheinberg, P. (1993). Vascular dementia Diagnostic criteria for research studies: Report of the NINDS-AIREN International Workshop*. *Neurology*, *43*(2), 250–250. https://doi.org/10.1212/WNL.43.2.250

Rombouts, S. A. R. B., Damoiseaux, J. S., Goekoop, R., Barkhof, F., Scheltens, P., Smith, S. M., & Beckmann, C. F. (2009). Model-Free Group Analysis Shows Altered BOLD FMRI Networks in Dementia. *Human Brain Mapping*, *30*, 256–266. https://doi.org/10.1002/hbm.20505

Rosenthal, R., & Rosnow, R. (1975). *The volunteer subject*. New York : Wiley. Retrieved from https://trove.nla.gov.au/version/26107489

Ross, D. E., Ochs, A. L., Seabaugh, J. M., Shrader, C. R., & Alzheimer's Disease Neuroimaging Initiative. (2013). Man versus machine: comparison of radiologists' interpretations and NeuroQuant® volumetric analyses of brain MRIs in patients with traumatic brain injury. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *25*(1), 32–39. https://doi.org/10.1176/appi.neuropsych.11120377

Rossor, M. N., Kennedy, A. M., & Frackowiak, R. S. (1996). Clinical and neuroimaging features of familial Alzheimer's disease. *Annals of the New York Academy of Sciences*, *777*, 49–56.

Rothstein, M. A. (2010). Is deidentification sufficient to protect health privacy in research? *The American Journal of Bioethics: AJOB*, *10*(9), 3–11. https://doi.org/10.1080/15265161.2010.494215

Rowe, C. C., Ackerman, U., Browne, W., Mulligan, R., Pike, K. L., O'Keefe, G., … Villemagne, V. L. (2008). Imaging of amyloid beta in Alzheimer's disease with 18F-BAY94-9172, a novel PET tracer: proof

of mechanism. *The Lancet. Neurology*, *7*(2), 129–135. https://doi.org/10.1016/S1474-4422(08)70001-2

Rowe, C. C., Ellis, K. A., Rimajova, M., Bourgeat, P., Pike, K. E., Jones, G., … Villemagne, V. L. (2010). Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. *Neurobiology of Aging*, *31*(8), 1275–1283. https://doi.org/10.1016/j.neurobiolaging.2010.04.007

Rowe, C. C., Ng, S., Ackermann, U., Gong, S. J., Pike, K., Savage, G., … Villemagne, V. L. (2007). Imaging beta-amyloid burden in aging and dementia. *Neurology*, *68*(20), 1718–1725. https://doi.org/10.1212/01.wnl.0000261919.22630.ea

Sachdev, P., Kalaria, R., O'Brien, J., Skoog, I., Alladi, S., Black, S. E., … Scheltens, P. (2014). Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. *Alzheimer Disease and Associated Disorders*, *28*(3), 206–218. https://doi.org/10.1097/WAD.0000000000000034

Salmon, E., Sadzot, B., Maquet, P., Degueldre, C., Lemaire, C., Rigo, P., … Franck, G. (1994). Differential diagnosis of Alzheimer's disease with PET. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine*, *35*(3), 391–398.

Samaille, T., Fillon, L., Cuingnet, R., Jouvent, E., Chabriat, H., Dormont, D., … Chupin, M. (2012). Contrast-Based Fully Automatic Segmentation of White Matter Hyperintensities: Method and Validation. *PLoS ONE*, *7*(11). https://doi.org/10.1371/journal.pone.0048953

Sämgård, K., Zetterberg, H., Blennow, K., Hansson, O., Minthon, L., & Londos, E. (2010). Cerebrospinal fluid total tau as a marker of Alzheimer's disease intensity. *International Journal of Geriatric Psychiatry*, *25*(4), 403–410. https://doi.org/10.1002/gps.2353

Samsi, K., & Manthorpe, J. (2014). Care pathways for dementia: current perspectives. *Clinical Interventions in Aging*, *9*, 2055–2063. https://doi.org/10.2147/CIA.S70628

Sanfilipo, M. P., Benedict, R. H. B., Zivadinov, R., & Bakshi, R. (2004). Correction for intracranial volume in analysis of whole brain atrophy in multiple sclerosis: the proportion vs. residual method. *NeuroImage*, *22*(4), 1732–1743. https://doi.org/10.1016/j.neuroimage.2004.03.037

Sarazin, M., Chauviré, V., Gerardin, E., Colliot, O., Kinkingnéhun, S., de Souza, L. C., … Dubois, B. (2010). The amnestic syndrome of hippocampal type in Alzheimer's disease: an MRI study. *Journal of Alzheimer's Disease: JAD*, *22*(1), 285–294. https://doi.org/10.3233/JAD-2010-091150

Satizabal, C., Beiser, A. S., & Seshadri, S. (2016). Incidence of Dementia over Three Decades in the Framingham Heart Study. *The New England Journal of Medicine*, *375*(1), 93–94. https://doi.org/10.1056/NEJMc1604823

Savva, G. M., Wharton, S. B., Ince, P. G., Forster, G., Matthews, F. E., Brayne, C., & Medical Research Council Cognitive Function and Ageing Study. (2009). Age, neuropathology, and dementia. *The New England Journal of Medicine*, *360*(22), 2302–2309. https://doi.org/10.1056/NEJMoa0806142

Sawyer, K., Corsentino, E., Sachs-Ericsson, N., & Steffens, D. C. (2012). Depression, hippocampal volume changes, and cognitive decline in a clinical sample of older depressed outpatients and non-depressed controls. *Aging & Mental Health*, *16*(6), 753–762. https://doi.org/10.1080/13607863.2012.678478

Scahill, R. I., Frost, C., Jenkins, R., Whitwell, J. L., Rossor, M. N., & Fox, N. C. (2003). A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. *Archives of Neurology*, *60*(7), 989–994. https://doi.org/10.1001/archneur.60.7.989

Scheltens, P., Barkhof, F., Leys, D., Pruvo, J. P., Nauta, J. J., Vermersch, P., … Valk, J. (1993). A semiquantative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. *Journal of the Neurological Sciences*, *114*(1), 7–12.

Scheltens, P., Barkhof, F., Leys, D., Wolters, E. C., Ravid, R., & Kamphorst, W. (1995). Histopathologic correlates of white matter changes on MRI in Alzheimer's disease and normal aging. *Neurology*, *45*(5), 883–888.

Scheltens, P., Blennow, K., Breteler, M. M. B., de Strooper, B., Frisoni, G. B., Salloway, S., & Van der Flier, W. M. (2016). Alzheimer's disease. *The Lancet*, *388*(10043), 505–517. https://doi.org/10.1016/S0140-6736(15)01124-1

Scheltens, P., Erkinjunti, T., Leys, D., Wahlund, L.-O., Inzitari, D., del Ser, T., … Pantoni, L. (1998). White Matter Changes on CT and MRI: An Overview of Visual Rating Scales. *European Neurology*, *39*(2), 80–89. https://doi.org/10.1159/000007921

Scheltens, P., Launer, L. J., Barkhof, F., Weinstein, H. C., & van Gool, W. A. (1995). Visual assessment of medial temporal lobe atrophy on magnetic resonance imaging: interobserver reliability. *Journal of Neurology*, *242*(9), 557–560.

Scheltens, P., Leys, D., Barkhof, F., Weinstein, H. C., Vermersch, P., Kuiper, M., … Valk, J. (1992). Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. *Journal of Neurology, Neurosurgery & Psychiatry*, *55*, 967–972.

Scheltens, P., & Rockwood, K. (2011). How golden is the gold standard of neuropathology in dementia? *Alzheimer's & Dementia*, *7*(4), 486–489. https://doi.org/10.1016/j.jalz.2011.04.011

Schiff, G. D., Kim, S., Abrams, R., Cosby, K., Lambert, B., Elstein, A. S., … McNutt, R. A. (2005). Diagnosing Diagnosis Errors: Lessons from a Multi-institutional Collaborative Project. In K. Henriksen, J. B. Battles, E. S. Marks, & D. I. Lewin (Eds.), *Advances in Patient Safety: From Research to Implementation (Volume 2: Concepts and Methodology)*. Rockville (MD): Agency for Healthcare Research and Quality (US). Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK20492/

Schmidt, P., Gaser, C., Arsic, M., Buck, D., Förschler, A., Berthele, A., … Mühlau, M. (2012). An automated tool for detection of FLAIR-hyperintense white-matter lesions in Multiple Sclerosis. *NeuroImage*, *59*(4), 3774–3783. https://doi.org/10.1016/j.neuroimage.2011.11.032

Schmidt, P., & Wink, L. (2017). LST: A lesion segmentation tool for SPM. Retrieved from http://www.statistical-modelling.de/LST_documentation.pdf

Schmitter, D., Roche, A., Maréchal, B., Ribes, D., Abdulkadir, A., Bach-Cuadra, M., … Krueger, G. (2015). An evaluation of volume-based morphometry for prediction of mild cognitive impairment and Alzheimer's disease. *NeuroImage: Clinical*, *7*, 7–17. https://doi.org/10.1016/j.nicl.2014.11.001

Schneider, J. A., Arvanitakis, Z., Bang, W., & Bennett, D. A. (2007). Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology*, *69*(24), 2197–2204.

Schneider, J. A., Boyle, P. A., Arvanitakis, Z., Bienias, J. L., & Bennett, D. A. (2007). Subcortical infarcts, Alzheimer's disease pathology, and memory function in older persons. *Annals of Neurology*, *62*(1), 59–66. https://doi.org/10.1002/ana.21142

Schöll, M., Lockhart, S. N., Schonhaut, D. R., O'Neil, J. P., Janabi, M., Ossenkoppele, R., … Jagust, W. J. (2016). PET Imaging of Tau Deposition in the Aging Human Brain. *Neuron*, *89*(5), 971–982. https://doi.org/10.1016/j.neuron.2016.01.028

Schönheit, B., Zarski, R., & Ohm, T. G. (2004). Spatial and temporal relationships between plaques and tangles in Alzheimer-pathology. *Neurobiology of Aging*, *25*(6), 697–711. https://doi.org/10.1016/j.neurobiolaging.2003.09.009

Schröder, J., & Pantel, J. (2016). Neuroimaging of hippocampal atrophy in early recognition of Alzheimer´s disease – a critical appraisal after two decades of research. *Psychiatry Research: Neuroimaging*, *247*, 71–78. https://doi.org/10.1016/j.pscychresns.2015.08.014

Schultz-Larsen, K., Kreiner, S., & Lomholt, R. K. (2007). Mini-Mental Status Examination: Mixed Rasch model item analysis derived two different cognitive dimensions of the MMSE. *Journal of Clinical Epidemiology*, *60*(3), 268–279. https://doi.org/10.1016/j.jclinepi.2006.06.007

Schwarz, A. J., Yu, P., Miller, B. B., Shcherbinin, S., Dickson, J., Navitsky, M., … Mintun, M. S. (2016). Regional profiles of the candidate tau PET ligand 18F-AV-1451 recapitulate key features of Braak histopathological stages. *Brain: A Journal of Neurology*, *139*(Pt 5), 1539–1550. https://doi.org/10.1093/brain/aww023

Ségonne, F., Dale, A. M., Busa, E., Glessner, M., Salat, D., Hahn, H. K., & Fischl, B. (2004). A hybrid approach to the skull stripping problem in MRI. *NeuroImage*, *22*(3), 1060–1075. https://doi.org/10.1016/j.neuroimage.2004.03.032

Ségonne, F., Pacheco, J., & Fischl, B. (2007). Geometrically accurate topology-correction of cortical surfaces using nonseparating loops. *IEEE Transactions on Medical Imaging*, *26*(4), 518–529. https://doi.org/10.1109/TMI.2006.887364

Seidman, L. J., Faraone, S. V., Goldstein, J. M., Goodman, J. M., Kremen, W. S., Toomey, R., … Tsuang, M. T. (1999). Thalamic and amygdala-hippocampal volume reductions in first-degree relatives of patients with schizophrenia: an MRI-based morphometric analysis. *Biological Psychiatry*, *46*(7), 941–954.

Sencakova, D., Graff-Radford, N. R., Willis, F. B., Lucas, J. A., Parfitt, F., Cha, R. H., … Clifford R. Jack, J. (2001). Hippocampal Atrophy Correlates With Clinical Features of Alzheimer Disease in African Americans. *Archives of Neurology*, *58*(10), 1593–1597. https://doi.org/10.1001/archneur.58.10.1593

Shaw, L. M., Vanderstichele, H., Knapik-Czajka, M., Clark, C. M., Aisen, P. S., Petersen, R. C., … Alzheimer's Disease Neuroimaging Initiative. (2009). Cerebrospinal fluid biomarker signature in

Alzheimer's disease neuroimaging initiative subjects. *Annals of Neurology*, *65*(4), 403–413. https://doi.org/10.1002/ana.21610

Sheline, Y. I., Morris, J. C., Snyder, A. Z., Price, J. L., Yan, Z., D'Angelo, G., … Mintun, M. A. (2010). APOE4 Allele Disrupts Resting State fMRI Connectivity in the Absence of Amyloid Plaques or Decreased CSF A 42. *Journal of Neuroscience*, *30*(50), 17035–17040. https://doi.org/10.1523/JNEUROSCI.3987-10.2010

Shpanskaya, K. S., Choudhury, K. R., Hostage, C., Murphy, K. R., Petrella, J. R., Doraiswamy, P. M., & Alzheimer's Disease Neuroimaging Initiative. (2014). Educational attainment and hippocampal atrophy in the Alzheimer's disease neuroimaging initiative cohort. *Journal of Neuroradiology. Journal De Neuroradiologie*, *41*(5), 350–357. https://doi.org/10.1016/j.neurad.2013.11.004

Simard, M. (1998). The mini-mental state examination: strengths and weaknesses of a clinical instrument. *The Canadian Alzheimer Disease Review*. Retrieved from http://stacommunications.com/customcomm/back-issue_pages/ad_review/adpdfs/december1998/10.pdf

Simmons, A., Westman, E., Muehlboeck, S., Mecocci, P., Vellas, B., Tsolaki, M., … for the AddNeuroMed Consortium. (2009). MRI Measures of Alzheimer's Disease and the AddNeuroMed Study. *Annals of the New York Academy of Sciences*, *1180*(1), 47–55. https://doi.org/10.1111/j.1749-6632.2009.05063.x

Simmons, A., Westman, E., Muehlboeck, S., Mecocci, P., Vellas, B., Tsolaki, M., … Spenger, C. (2011). The AddNeuroMed framework for multi-centre MRI assessment of Alzheimer's disease : experience from the first 24 months. *International Journal of Geriatric Psychiatry*, *26*(1), 75–82. https://doi.org/10.1002/gps.2491

Singh, H., Naik, A. D., Rao, R., & Petersen, L. A. (2008). Reducing Diagnostic Errors through Effective Communication: Harnessing the Power of Information Technology. *Journal of General Internal Medicine*, *23*(4), 489–494. https://doi.org/10.1007/s11606-007-0393-z

Sjöbeck, M., Haglund, M., & Englund, E. (2006). White matter mapping in Alzheimer's disease: A neuropathological study. *Neurobiology of Aging*, *27*(5), 673–680. https://doi.org/10.1016/j.neurobiolaging.2005.03.007

Sjögren, M., Davidsson, P., Tullberg, M., Minthon, L., Wallin, A., Wikkelso, C., … Blennow, K. (2001). Both total and phosphorylated tau are increased in Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *70*(5), 624–630. https://doi.org/10.1136/jnnp.70.5.624

Slavin, M. J., Sandstrom, C. K., Tran, T.-T. T., Doraiswamy, P. M., & Petrella, J. R. (2007). Hippocampal volume and the Mini-Mental State Examination in the diagnosis of amnestic mild cognitive impairment. *AJR. American Journal of Roentgenology*, *188*(5), 1404–1410. https://doi.org/10.2214/AJR.06.1052

Sled, J. G., Zijdenbos, A. P., & Evans, A. C. (1998). A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Transactions on Medical Imaging*, *17*(1), 87–97. https://doi.org/10.1109/42.668698

Small, S. A., Schobel, S. A., Buxton, R. B., Witter, M. P., & Barnes, C. A. (2011). A pathophysiological framework of hippocampal dysfunction in ageing and disease. *Nature Reviews Neuroscience*, *12*(10), 585–601. https://doi.org/10.1038/nrn3085

Smart, S. D., Firbank, M. J., & O'Brien, J. T. (2011). Validation of Automated White Matter Hyperintensity Segmentation. *Journal of Aging Research*, *2011*. https://doi.org/10.4061/2011/391783

Smith, C. D., Snowdon, D. A., Wang, H., & Markesbery, W. R. (2000). White matter volumes and periventricular white matter hyperintensities in aging and dementia. *Neurology*, *54*(4), 838–842.

Smith, E. E., Egorova, S., Blacker, D., Killiany, R. J., Muzikansky, A., Dickerson, B. C., … Guttmann, C. R. G. (2008). Magnetic resonance imaging white matter hyperintensities and brain volume in the prediction of mild cognitive impairment and dementia. *Archives of Neurology*, *65*(1), 94–100. https://doi.org/10.1001/archneurol.2007.23

Smith, E. E., & Eichler, F. (2006). Cerebral amyloid angiopathy and lobar intracerebral hemorrhage. *Archives of Neurology*, *63*(1), 148–151. https://doi.org/10.1001/archneur.63.1.148

Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., … Beckmann, C. F. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences*, *106*(31), 13040–13045. https://doi.org/10.1073/pnas.0905267106

Snowdon, D. A., Greiner, L. H., Mortimer, J. A., Riley, K. P., Greiner, P. A., & Markesbery, W. R. (1997). Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. *JAMA*, *277*(10), 813–817.

Soares, D. P., & Law, M. (2009). Magnetic resonance spectroscopy of the brain: review of metabolites and clinical applications. *Clinical Radiology*, *64*(1), 12–21. https://doi.org/10.1016/j.crad.2008.07.002

Sojkova, J., Zhou, Y., An, Y., Kraut, M. A., Ferrucci, L., Wong, D. F., & Resnick, S. M. (2011). Longitudinal patterns of β-amyloid deposition in nondemented older adults. *Archives of Neurology*, *68*(5), 644–649. https://doi.org/10.1001/archneurol.2011.77

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., … Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, *7*(3), 280–292. https://doi.org/10.1016/j.jalz.2011.03.003

Sperling, R. A., LaViolette, P. S., O'Keefe, K., O'Brien, J., Rentz, D. M., Pihlajamaki, M., … Johnson, K. A. (2009). Amyloid Deposition Is Associated with Impaired Default Network Function in Older Persons without Dementia. *Neuron*, *63*(2), 178–188. https://doi.org/10.1016/j.neuron.2009.07.003

Spulber, G., Simmons, A., Muehlboeck, J.-S., Mecocci, P., Vellas, B., Tsolaki, M., … for the AddNeuroMed consortium and for the Alzheimer Disease Neuroimaging Initiative. (2013). An MRI-based index to measure the severity of Alzheimer's disease-like structural pattern in subjects with mild cognitive impairment. *Journal of Internal Medicine*, *273*(4), 396–409. https://doi.org/10.1111/joim.12028

Steffens, D. C., Payne, M. E., Greenberg, D. L., Byrum, C. E., Welsh-Bohmer, K. A., Wagner, H. R., & MacFall, J. R. (2002). Hippocampal volume and incident dementia in geriatric depression. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *10*(1), 62–71.

Stenset, V., Hofoss, D., Berstad, A. E., Negaard, A., Gjerstad, L., & Fladby, T. (2008). White Matter Lesion Subtypes and Cognitive Deficits in Patients with Memory Impairment. *Dementia and Geriatric Cognitive Disorders*, *26*(5), 424–431. https://doi.org/10.1159/000165355

Stewart, R., Soremekun, M., Perera, G., Broadbent, M., Callard, F., Denis, M., … Lovestone, S. (2009). The South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) case register: development and descriptive data. *BMC Psychiatry*, *9*(1), 51. https://doi.org/10.1186/1471-244X-9-51

Stoub, T. R., Rogalski, E. J., Leurgans, S., Bennett, D. A., & deToledo-Morrell, L. (2010). Rate of entorhinal and hippocampal atrophy in incipient and mild AD: Relation to memory function. *Neurobiology of Aging*, *31*(7), 1089–1098. https://doi.org/10.1016/j.neurobiolaging.2008.08.003

Strozyk, D., Blennow, K., White, L. R., & Launer, L. J. (2003). CSF Abeta 42 levels correlate with amyloid-neuropathology in a population-based autopsy study. *Neurology*, *60*(4), 652–656.

Suppa, P., Anker, U., Spies, L., Bopp, I., Rüegger-Frey, B., Klaghofer, R., … Buchert, R. (2015). Fully automated atlas-based hippocampal volumetry for detection of Alzheimer's disease in a memory clinic setting. *Journal of Alzheimer's Disease: JAD*, *44*(1), 183–193. https://doi.org/10.3233/JAD-141446

Svärd, D., Nilsson, M., Lampinen, B., Lätt, J., Sundgren, P. C., Stomrud, E., … van Westen, D. (2017). The effect of white matter hyperintensities on statistical analysis of diffusion tensor imaging in cognitively healthy elderly and prodromal Alzheimer's disease. *PLoS ONE*, *12*(9). https://doi.org/10.1371/journal.pone.0185239

Tabatabaei-Jafari, H., Shaw, M. E., & Cherbuin, N. (2015). Cerebral atrophy in mild cognitive impairment: A systematic review with meta-analysis. *Alzheimer's & Dementia (Amsterdam, Netherlands)*, *1*(4), 487–504. https://doi.org/10.1016/j.dadm.2015.11.002

Tapiola, T., Alafuzoff, I., Herukka, S.-K., Parkkinen, L., Hartikainen, P., Soininen, H., & Pirttilä, T. (2009). Cerebrospinal Fluid β-Amyloid 42 and Tau Proteins as Biomarkers of Alzheimer-Type Pathologic Changes in the Brain. *Archives of Neurology*, *66*(3), 382–389. https://doi.org/10.1001/archneurol.2008.596

Taylor, W. D., McQuoid, D. R., Payne, M. E., Zannas, A. S., MacFall, J. R., & Steffens, D. C. (2014). Hippocampus atrophy and the longitudinal course of late-life depression. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *22*(12), 1504–1512. https://doi.org/10.1016/j.jagp.2013.11.004

Thambisetty, M., Simmons, A., Velayudhan, L., Hye, A., Campbell, J., Zhang, Y., … Lovestone, S. (2010). Association of plasma clusterin concentration with severity, pathology, and progression in

Alzheimer disease. *Archives of General Psychiatry*, *67*(7), 739–748. https://doi.org/10.1001/archgenpsychiatry.2010.78

The Academy of Medical Sciences. (2006, January). Personal data for public good: using health information in medical research. Retrieved from http://www.acmedsci.ac.uk/policy/policy-projects/personal-data/

Troncoso, J. C., Zonderman, A. B., Resnick, S. M., Crain, B., Pletnikova, O., & O'Brien, R. J. (2008). Effect of infarcts on dementia in the Baltimore longitudinal study of aging. *Annals of Neurology*, *64*(2), 168–176. https://doi.org/10.1002/ana.21413

Trygg, J., & Wold, S. (2002). Orthogonal projections to latent structures (O-PLS). *Journal of Chemometrics*, *16*(3), 119–128. https://doi.org/10.1002/cem.695

Tuladhar, A. M., Reid, A. T., Shumskaya, E., Laat, K. F. de, Norden, A. G. W. van, Dijk, E. J. van, … Leeuw, F.-E. de. (2015). Relationship Between White Matter Hyperintensities, Cortical Thickness, and Cognition. *Stroke*, *46*(2), 425–432. https://doi.org/10.1161/STROKEAHA.114.007146

Urs, R., Potter, E., Barker, W., Appel, J., Loewenstein, D. A., Zhao, W., & Duara, R. (2009). Visual rating system for assessing magnetic resonance images: a tool in the diagnosis of mild cognitive impairment and Alzheimer disease. *Journal of Computer Assisted Tomography*, *33*(1), 73–78.

Valdés Hernández, M. del C., Booth, T., Murray, C., Gow, A. J., Penke, L., Morris, Z., … Wardlaw, J. M. (2013). Brain white matter damage in aging and cognitive ability in youth and older age. *Neurobiology of Aging*, *34*(12), 2740–2747. https://doi.org/10.1016/j.neurobiolaging.2013.05.032

Valenti, R., Pantoni, L., & Markus, H. S. (2014). Treatment of vascular risk factors in patients with a diagnosis of Alzheimer's disease: a systematic review. *BMC Medicine*, *12*, 160. https://doi.org/10.1186/s12916-014-0160-z

van der Flier, W. M., van Buchem, M. A., Weverling-Rijnsburger, A. W. E., Mutsaers, E. R., Bollen, E. L. E. M., Admiraal-Behloul, F., … Middelkoop, H. A. M. (2004). Memory complaints in patients with normal cognition are associated with smaller hippocampal volumes. *Journal of Neurology*, *251*(6), 671–675. https://doi.org/10.1007/s00415-004-0390-7

van der Lijn, F., Verhaaren, B. F. J., Ikram, M. A., Klein, S., de Bruijne, M., Vrooman, H. A., … Niessen, W. J. (2012). Automated measurement of local white matter lesion volume. *NeuroImage*, *59*(4), 3901–3908. https://doi.org/10.1016/j.neuroimage.2011.11.021

van Vliet, D., de Vugt, M. E., Bakker, C., Pijnenburg, Y. a. L., Vernooij-Dassen, M. J. F. J., Koopmans, R. T. C. M., & Verhey, F. R. J. (2013). Time to diagnosis in young-onset dementia as compared with late-onset dementia. *Psychological Medicine*, *43*(2), 423–432. https://doi.org/10.1017/S0033291712001122

Vandenberghe, R., Van Laere, K., Ivanoiu, A., Salmon, E., Bastin, C., Triau, E., … Brooks, D. J. (2010). 18F-flutemetamol amyloid imaging in Alzheimer disease and mild cognitive impairment: a phase 2 trial. *Annals of Neurology*, *68*(3), 319–329. https://doi.org/10.1002/ana.22068

Varon, D., Barker, W., Loewenstein, D., Greig, M., Bohorquez, A., Santos, I., … Alzheimer's Disease Neuroimaging Initiative. (2015). Visual rating and volumetric measurement of medial temporal atrophy in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort: baseline diagnosis and the prediction of MCI outcome. *International Journal of Geriatric Psychiatry*, *30*(2), 192–200. https://doi.org/10.1002/gps.4126

Velayudhan, L., Ryu, S.-H., Raczek, M., Philpot, M., Lindesay, J., Critchfield, M., & Livingston, G. (2014). Review of brief cognitive tests for patients with suspected dementia. *International Psychogeriatrics / Ipa*, *26*(8), 1247–1262. https://doi.org/10.1017/S1041610214000416

Vertesi, A., Lever, J. A., Molloy, D. W., Sanderson, B., Tuttle, I., Pokoradi, L., & Principi, E. (2001). Standardized Mini-Mental State Examination. Use and interpretation. *Canadian Family Physician*, *47*, 2018–2023.

Vestergaard, M. B., Lindberg, U., Aachmann-Andersen, N. J., Lisbjerg, K., Christensen, S. J., Law, I., … Larsson, H. B. (2016). Acute hypoxia increases the cerebral metabolic rate - a magnetic resonance imaging study. *Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, *36*(6), 1046–1058. https://doi.org/10.1177/0271678X15606460

Vieira, R. T., Caixeta, L., Machado, S., Silva, A. C., Nardi, A. E., Arias-Carrión, O., & Carta, M. G. (2013). Epidemiology of early-onset dementia: a review of the literature. *Clinical Practice and Epidemiology in Mental Health: CP & EMH*, *9*, 88–95. https://doi.org/10.2174/1745017901309010088

Villemagne, V. L., & Chételat, G. (2016). Neuroimaging biomarkers in Alzheimer's disease and other dementias. *Ageing Research Reviews*, *30*, 4–16. https://doi.org/10.1016/j.arr.2016.01.004

Villemagne, V. L., Doré, V., Bourgeat, P., Burnham, S. C., Laws, S., Salvado, O., … Rowe, C. C. (2017). Aβ-amyloid and Tau Imaging in Dementia. *Seminars in Nuclear Medicine*, *47*(1), 75–88. https://doi.org/10.1053/j.semnuclmed.2016.09.006

Villemagne, V. L., Ong, K., Mulligan, R. S., Holl, G., Pejoska, S., Jones, G., … Rowe, C. C. (2011). Amyloid imaging with (18)F-florbetaben in Alzheimer disease and other dementias. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine*, *52*(8), 1210–1217. https://doi.org/10.2967/jnumed.111.089730

Visser, P. J., Scheltens, P., Verhey, F. R., Schmand, B., Launer, L. J., Jolles, J., & Jonker, C. (1999). Medial temporal lobe atrophy and memory dysfunction as predictors for dementia in subjects with mild cognitive impairment. *Journal of Neurology*, *246*(6), 477–485.

Visser, P. J., Verhey, F., Knol, D. L., Scheltens, P., Wahlund, L.-O., Freund-Levi, Y., … Blennow, K. (2009). Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective cohort study. *The Lancet. Neurology*, *8*(7), 619–627. https://doi.org/10.1016/S1474-4422(09)70139-5

Viswanathan, A., & Chabriat, H. (2006). Cerebral Microhemorrhage. *Stroke*, *37*(2), 550–555. https://doi.org/10.1161/01.STR.0000199847.96188.12

Voevodskaya, O., Simmons, A., Nordenskjöld, R., Kullberg, J., Ahlström, H., Lind, L., … Alzheimer's Disease Neuroimaging Initiative. (2014). The effects of intracranial volume adjustment approaches on multiple regional MRI volumes in healthy aging and Alzheimer's disease. *Frontiers in Aging Neuroscience*, *6*, 264. https://doi.org/10.3389/fnagi.2014.00264

Wahlund, L. O., Barkhof, F., Fazekas, F., Bronge, L., Augustin, M., Sjogren, M., … Scheltens, P. (2001). A New Rating Scale for Age-Related White Matter Changes Applicable to MRI and CT. *Stroke*, *32*(6), 1318–1322. https://doi.org/10.1161/01.STR.32.6.1318

Wahlund, L.-O., Julin, P., Johansson, S.-E., & Scheltens, P. (2000). Visual rating and volumetry of the medial temporal lobe on magnetic resonance imaging in dementia: a comparative study. *Journal of Neurology, Neurosurgery & Psychiatry*, *69*(5), 630–635.

Wahlund, L.-O., Junlin, P., Lindqvist, J., & Scheltens, P. (1999). Visual assessment of medial temporal lobe atrophy in demented and healthy control subjects: correlation with volumetry. *Psychiatry Research: Neuroimaging*, *90*, 193–199.

Wahlund, L.-O., Westman, E., van Westen, D., Wallin, A., Shams, S., Cavallin, L., & Larsson, E.-M. (2016). Imaging biomarkers of dementia: recommended visual rating scales with teaching cases. *Insights into Imaging*, *8*(1), 79–90. https://doi.org/10.1007/s13244-016-0521-6

Wallin, Å. K., Hansson, O., Blennow, K., Londos, E., & Minthon, L. (2009). Can CSF biomarkers or pre-treatment progression rate predict response to cholinesterase inhibitor treatment in Alzheimer's disease? *International Journal of Geriatric Psychiatry*, *24*(6), 638–647. https://doi.org/10.1002/gps.2195

Wang, L., Zang, Y., He, Y., Liang, M., Zhang, X., Tian, L., … Li, K. (2006). Changes in hippocampal connectivity in the early stages of Alzheimer's disease: Evidence from resting state fMRI. *NeuroImage*, *31*(2), 496–504. https://doi.org/10.1016/j.neuroimage.2005.12.033

Wardlaw, J. M., Smith, E. E., Biessels, G. J., Cordonnier, C., Fazekas, F., Frayne, R., … Dichgans, M. (2013). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *The Lancet Neurology*, *12*(8), 822–838. https://doi.org/10.1016/S1474-4422(13)70124-8

Wattjes, M. P., Henneman, W. J. P., van der Flier, W. M., de Vries, O., Geurts, J. J. G., Scheltens, P., … Barkhof, F. (2009). Diagnostic Imaging of Patients in a Memory Clinic: Comparison of MR Imaging and 64 –Detector Row CT. *Radiology*, *253*(1), 174–183.

Weih, M., Degirmenci, Ü., Kreil, S., Lewczuk, P., Schmidt, D., Kornhuber, J., & Kuwert, T. (2010). Perfusion Imaging with SPECT in the Era of Pathophysiology-Based Biomarkers for Alzheimer's Disease. *International Journal of Alzheimer's Disease*, *2010*. https://doi.org/10.4061/2010/109618

Weimer, D. L., & Sager, M. A. (2009). Early identification and treatment of Alzheimer's disease: social and fiscal outcomes. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *5*(3), 215–226. https://doi.org/10.1016/j.jalz.2009.01.028

Weiner, M. W., Veitch, D. P., Aisen, P. S., Beckett, L. A., Cairns, N. J., Cedarbaum, J., … Trojanowski, J. Q. (2015). Impact of the Alzheimer's Disease Neuroimaging Initiative, 2004 to 2014. *Alzheimer's &*

Dementia : The Journal of the Alzheimer's Association, *11*(7), 865–884. https://doi.org/10.1016/j.jalz.2015.04.005

West, M. J., Coleman, P. D., Flood, D. G., & Troncoso, J. C. (1994). Differences in the pattern of hippocampal neuronal loss in normal ageing and Alzheimer's disease. *Lancet (London, England)*, *344*(8925), 769–772.

Westman, E., Aguilar, C., Muehlboeck, J.-S., & Simmons, A. (2013). Regional Magnetic Resonance Imaging Measures for Multivariate Analysis in Alzheimer's Disease and Mild Cognitive Impairment. *Brain Topography*, *26*(1), 9–23. https://doi.org/10.1007/s10548-012-0246-x

Westman, E., Cavallin, L., Muehlboeck, J.-S., Zhang, Y., Mecocci, P., Vellas, B., … AddNeuroMed consortium. (2011a). Sensitivity and specificity of medial temporal lobe visual ratings and multivariate regional MRI classification in Alzheimer's disease. *PloS One*, *6*(7), e22506. https://doi.org/10.1371/journal.pone.0022506

Westman, E., Cavallin, L., Muehlboeck, J.-S., Zhang, Y., Mecocci, P., Vellas, B., … for the AddNeuroMed consortium. (2011b). Sensitivity and Specificity of Medial Temporal Lobe Visual Ratings and Multivariate Regional MRI Classification in Alzheimer's Disease. *PLoS ONE*, *6*(7), e22506. https://doi.org/10.1371/journal.pone.0022506

Westman, E., Muehlboeck, J.-S., & Simmons, A. (2012). Combining MRI and CSF measures for classification of Alzheimer's disease and prediction of mild cognitive impairment conversion. *NeuroImage*, *62*(1), 229–238. https://doi.org/10.1016/j.neuroimage.2012.04.056

Westman, E., Simmons, A., Muehlboeck, J.-S., Mecocci, P., Vellas, B., Tsolaki, M., … Wahlund, L.-O. (2011). AddNeuroMed and ADNI: Similar patterns of Alzheimer's atrophy and automated MRI classification accuracy in Europe and North America. *NeuroImage*, *58*(3), 818–828. https://doi.org/10.1016/j.neuroimage.2011.06.065

Westman, E., Simmons, A., Zhang, Y., Muehlboeck, J.-S., Tunnard, C., Liu, Y., … Wahlund, L.-O. (2011). Multivariate analysis of MRI data for Alzheimer's disease, mild cognitive impairment and healthy controls. *NeuroImage*, *54*(2), 1178–1187. https://doi.org/10.1016/j.neuroimage.2010.08.044

Westman, E., Spenger, C., Öberg, J., Reyer, H., Pahnke, J., & Wahlund, L.-O. (2009). In vivo 1H-magnetic resonance spectroscopy can detect metabolic changes in APP/PS1 mice after donepezil treatment. *BMC Neuroscience*, *10*, 33. https://doi.org/10.1186/1471-2202-10-33

Westman, E., Wahlund, L.-O., Foy, C., Poppe, M., Cooper, A., Murphy, D., … Simmons, A. (2011). Magnetic Resonance Imaging and Magnetic Resonance Spectroscopy for Detection of Early Alzheimer's Disease. *Journal of Alzheimer's Disease*, *26*(s3), 307–319. https://doi.org/10.3233/JAD-2011-0028

White, L. (2009). Brain lesions at autopsy in older Japanese-American men as related to cognitive impairment and dementia in the final years of life: a summary report from the Honolulu-Asia aging study. *Journal of Alzheimer's Disease: JAD*, *18*(3), 713–725. https://doi.org/10.3233/JAD-2009-1178

Whitwell, J. L., Crum, W. R., Watt, H. C., & Fox, N. C. (2001). Normalization of cerebral volumes by use of intracranial volume: implications for longitudinal quantitative MR imaging. *AJNR. American Journal of Neuroradiology*, *22*(8), 1483–1489.

Whitwell, J. L., Wiste, H. J., Weigand, S. D., Rocca, W. A., Knopman, D. S., Roberts, R. O., … Jack, C. R. (2012). Comparison of imaging biomarkers in ADNI versus the Mayo Clinic Study of Aging. *Archives of Neurology*, *69*(5), 614–622. https://doi.org/10.1001/archneurol.2011.3029

Wierenga, C. E., Hays, C. C., & Zlatar, Z. Z. (2014). Cerebral blood flow measured by arterial spin labeling MRI as a preclinical marker of Alzheimer's disease. *Journal of Alzheimer's Disease: JAD*, *42 Suppl 4*, S411-419. https://doi.org/10.3233/JAD-141467

Wiklund, S., Johansson, E., Sjöström, L., Mellerowicz, E. J., Edlund, U., Shockcor, J. P., … Trygg, J. (2008). Visualization of GC/TOF-MS-Based Metabolomics Data for Identification of Biochemically Interesting Compounds Using OPLS Class Models. *Analytical Chemistry*, *80*(1), 115–122. https://doi.org/10.1021/ac0713510

Wilcock, J., Iliffe, S., Griffin, M., Jain, P., Thuné-Boyle, I., Lefford, F., & Rapp, D. (2013). Tailored educational intervention for primary care to improve the management of dementia: the EVIDEM-ED cluster randomized controlled trial. *Trials*, *14*, 397. https://doi.org/10.1186/1745-6215-14-397

Wingo, T. S., Lah, J. J., Levey, A. I., & Cutler, D. J. (2012). Autosomal Recessive Causes Likely in Early-Onset Alzheimer Disease. *Archives of Neurology*, *69*(1), 59–64. https://doi.org/10.1001/archneurol.2011.221

Wolf, H., Grunwald, M., Kruggel, F., Riedel-Heller, S. G., Angerhöfer, S., Hojjatoleslami, A., … Gertz, H. (2001). Hippocampal volume discriminates between normal cognition; questionable and mild dementia in the elderly. *Neurobiology of Aging*, *22*(2), 177–186.

Wolz, R., Aljabar, P., Hajnal, J. V., Hammers, A., Rueckert, D., & Alzheimer's Disease Neuroimaging Initiative. (2010). LEAP: learning embeddings for atlas propagation. *NeuroImage*, *49*(2), 1316–1325. https://doi.org/10.1016/j.neuroimage.2009.09.069

Wong, D. F., Rosenberg, P. B., Zhou, Y., Kumar, A., Raymont, V., Ravert, H. T., … Pontecorvo, M. J. (2010). In vivo imaging of amyloid deposition in Alzheimer disease using the radioligand 18F-AV-45 (florbetapir [corrected] F 18). *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine*, *51*(6), 913–920. https://doi.org/10.2967/jnumed.109.069088

World Health Organization, & International Programme on Chemical Safety. (2001). Biomarkers in risk assessment : validity and validation. World Health Organization.

Wu, X., Li, R., Fleisher, A. S., Reiman, E. M., Guan, X., Zhang, Y., … Yao, L. (2011). Altered default mode network connectivity in alzheimer's disease-A resting functional MRI and bayesian network study. *Human Brain Mapping*, *32*(11), 1868–1881. https://doi.org/10.1002/hbm.21153

Xiong, Y. Y., & Mok, V. (2011). Age-Related White Matter Changes [Research article]. https://doi.org/10.4061/2011/617927

Yavuz, B. B., Ariogul, S., Cankurtaran, M., Oguz, K. K., Halil, M., Dagli, N., & Cankurtaran, E. S. (2007). Hippocampal atrophy correlates with the severity of cognitive decline. *International Psychogeriatrics*, *19*(4), 767–777. https://doi.org/10.1017/S1041610206004303

Yoshita, M., Fletcher, E., Harvey, D., Ortega, M., Martinez, O., Mungas, D. M., … DeCarli, C. S. (2006). Extent and distribution of white matter hyperintensities in normal aging, MCI, and AD. *Neurology*, *67*(12), 2192–2198. https://doi.org/10.1212/01.wnl.0000249119.95747.1f

Ystad, M. A., Lundervold, A. J., Wehling, E., Espeseth, T., Rootwelt, H., Westlye, L. T., … Lundervold, A. (2009). Hippocampal volumes are important predictors for memory function in elderly women. *BMC Medical Imaging*, *9*, 17. https://doi.org/10.1186/1471-2342-9-17

Yu, P., Sun, J., Wolz, R., Stephenson, D., Brewer, J., Fox, N. C., … Schwarz, A. J. (2014). Operationalizing hippocampal volume as an enrichment biomarker for amnestic mild cognitive impairment trials: effect of algorithm, test-retest variability, and cut point on trial cost, duration, and sample size. *Neurobiology of Aging*, *35*(4), 808–818. https://doi.org/10.1016/j.neurobiolaging.2013.09.039

Zekry, D., Hauw, J.-J., & Gold, G. (2002). Mixed Dementia: Epidemiology, Diagnosis, and Treatment. *Journal of the American Geriatrics Society*, *50*(8), 1431–1438. https://doi.org/10.1046/j.1532-5415.2002.50367.x

Zhang, H.-Y., Wang, S.-J., Lui, B., Ma, Z.-L., Yang, M., Zhang, Z.-J., & Teng, G.-J. (2010). Resting Brain Connectivity: Changes during the Progress of Alzheimer Disease. *Radiology*, *256*(2), 598–606.

Zhou, Q., Goryawala, M., Cabrerizo, M., Barker, W., Duara, R., & Adjouadi, M. (2014). Significance of normalization on anatomical MRI measures in predicting Alzheimer's disease. *TheScientificWorldJournal*, *2014*, 541802. https://doi.org/10.1155/2014/541802

APPENDICES

APPENDIX 1

Chapter 3: Group differences (male versus female) in age, average MMSE, and total normalised hippocampal volume in the portion of the BRC memory clinic cohort used in chapter 3 study, as measured by ANOVA. $P < 0.05$ is considered statistically significant.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
norm total HC	Between Groups	.000	1	.000	7.311	.007
	Within Groups	.000	534	.000		
	Total	.000	535			
age at MMSE	Between Groups	54.927	1	54.927	.524	.469
	Within Groups	55946.458	534	104.769		
	Total	56001.385	535			
MMSE	Between Groups	25.059	1	25.059	.950	.330
	Within Groups	14087.001	534	26.380		
	Total	14112.060	535			

APPENDIX 2

Chapter 4: Group differences (between diagnostic categories) in age and average MMSE in the portion of BRC memory clinic cohort used in the chapter 4 study, as measured by ANOVA and Bonferroni's post-hoc tests. $P < 0.05$ is considered statistically significant.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
MMSE score	Between Groups	2036.155	8	254.519	12.361	.000
	Within Groups	9759.725	474	20.590		
	Total	11795.880	482			
age	Between Groups	15087.518	8	1885.940	20.995	.000
	Within Groups	59196.762	659	89.828		
	Total	74284.280	667			

Multiple Comparisons

Bonferroni

Dependent Variable	(I) primary dx category	(J) primary dx category	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
MMSE score	diagnosis not listed	no diagnosis	-.365	1.292	1.000	-4.52	3.79
		AD	3.491*	.572	.000	1.65	5.33
		MCI	-1.055	.744	1.000	-3.45	1.34
		Mixed Dementia	3.658*	.823	.000	1.01	6.30
		VaD	4.680*	1.065	.000	1.26	8.10
		unspecified dementia	5.200*	1.046	.000	1.84	8.56
		other dementia	5.635*	1.502	.007	.80	10.47
		other psychiatric disorder	1.675	.786	1.000	-.85	4.20

	no diagnosis	diagnosis not listed	.365	1.292	1.000	-3.79	4.52
		AD	3.856	1.265	.087	-.21	7.92
		MCI	-.690	1.351	1.000	-5.04	3.66
		Mixed Dementia	4.023	1.396	.149	-.47	8.51
		VaD	5.045*	1.551	.044	.06	10.03
		unspecified dementia	5.565*	1.538	.012	.62	10.51
		other dementia	6.000	1.879	.054	-.04	12.04
		other psychiatric disorder	2.041	1.375	1.000	-2.38	6.46
	AD	diagnosis not listed	-3.491*	.572	.000	-5.33	-1.65
		no diagnosis	-3.856	1.265	.087	-7.92	.21
		MCI	-4.546*	.695	.000	-6.78	-2.31
		Mixed Dementia	.167	.779	1.000	-2.34	2.67
		VaD	1.189	1.032	1.000	-2.13	4.51
		unspecified dementia	1.709	1.012	1.000	-1.55	4.96
		other dementia	2.144	1.479	1.000	-2.61	6.90
		other psychiatric disorder	-1.815	.741	.527	-4.20	.57
	MCI	diagnosis not listed	1.055	.744	1.000	-1.34	3.45
		no diagnosis	.690	1.351	1.000	-3.66	5.04
		AD	4.546*	.695	.000	2.31	6.78
		Mixed Dementia	4.713*	.913	.000	1.78	7.65
		VaD	5.735*	1.136	.000	2.08	9.39
		unspecified dementia	6.255*	1.118	.000	2.66	9.85
		other dementia	6.690*	1.554	.001	1.69	11.69
		other psychiatric disorder	2.730	.880	.074	-.10	5.56
	Mixed Dementia	diagnosis not listed	-3.658*	.823	.000	-6.30	-1.01
		no diagnosis	-4.023	1.396	.149	-8.51	.47
		AD	-.167	.779	1.000	-2.67	2.34

		MCI	-4.713*	.913	.000	-7.65	-1.78
		VaD	1.022	1.189	1.000	-2.80	4.85
		unspecified dementia	1.542	1.172	1.000	-2.23	5.31
		other dementia	1.977	1.593	1.000	-3.15	7.10
		other psychiatric disorder	-1.982	.948	1.000	-5.03	1.07
	VaD	diagnosis not listed	-4.680*	1.065	.000	-8.10	-1.26
		no diagnosis	-5.045*	1.551	.044	-10.03	-.06
		AD	-1.189	1.032	1.000	-4.51	2.13
		MCI	-5.735*	1.136	.000	-9.39	-2.08
		Mixed Dementia	-1.022	1.189	1.000	-4.85	2.80
		unspecified dementia	.520	1.353	1.000	-3.83	4.87
		other dementia	.955	1.731	1.000	-4.61	6.52
		other psychiatric disorder	-3.005	1.165	.366	-6.75	.74
	unspecified dementia	diagnosis not listed	-5.200*	1.046	.000	-8.56	-1.84
		no diagnosis	-5.565*	1.538	.012	-10.51	-.62
		AD	-1.709	1.012	1.000	-4.96	1.55
		MCI	-6.255*	1.118	.000	-9.85	-2.66
		Mixed Dementia	-1.542	1.172	1.000	-5.31	2.23
		VaD	-.520	1.353	1.000	-4.87	3.83
		other dementia	.435	1.719	1.000	-5.09	5.96
		other psychiatric disorder	-3.524	1.147	.081	-7.21	.16
	other dementia	diagnosis not listed	-5.635*	1.502	.007	-10.47	-.80
		no diagnosis	-6.000	1.879	.054	-12.04	.04
		AD	-2.144	1.479	1.000	-6.90	2.61
		MCI	-6.690*	1.554	.001	-11.69	-1.69
		Mixed Dementia	-1.977	1.593	1.000	-7.10	3.15
		VaD	-.955	1.731	1.000	-6.52	4.61

		unspecified dementia	-.435	1.719	1.000	-5.96	5.09
		other psychiatric disorder	-3.959	1.575	.441	-9.02	1.10
	other psychiatric disorder	diagnosis not listed	-1.675	.786	1.000	-4.20	.85
		no diagnosis	-2.041	1.375	1.000	-6.46	2.38
		AD	1.815	.741	.527	-.57	4.20
		MCI	-2.730	.880	.074	-5.56	.10
		Mixed Dementia	1.982	.948	1.000	-1.07	5.03
		VaD	3.005	1.165	.366	-.74	6.75
		unspecified dementia	3.524	1.147	.081	-.16	7.21
		other dementia	3.959	1.575	.441	-1.10	9.02
age	diagnosis not listed	no diagnosis	-6.944*	2.064	.029	-13.57	-.32
		AD	-10.403*	1.044	.000	-13.75	-7.05
		MCI	-8.259*	1.290	.000	-12.40	-4.12
		Mixed Dementia	-12.367*	1.446	.000	-17.01	-7.72
		VaD	-11.875*	1.968	.000	-18.19	-5.56
		unspecified dementia	-5.970*	1.841	.045	-11.88	-.06
		other dementia	-2.204	3.106	1.000	-12.18	7.77
		other psychiatric disorder	-.345	1.383	1.000	-4.79	4.10
	no diagnosis	diagnosis not listed	6.944*	2.064	.029	.32	13.57
		AD	-3.459	2.004	1.000	-9.89	2.98
		MCI	-1.316	2.143	1.000	-8.19	5.56
		Mixed Dementia	-5.423	2.240	.567	-12.62	1.77
		VaD	-4.931	2.608	1.000	-13.30	3.44
		unspecified dementia	.973	2.513	1.000	-7.09	9.04
		other dementia	4.740	3.546	1.000	-6.65	16.13
		other psychiatric disorder	6.598	2.200	.101	-.47	13.66
	AD	diagnosis not listed	10.403*	1.044	.000	7.05	13.75

	no diagnosis	3.459	2.004	1.000	-2.98	9.89
	MCI	2.144	1.192	1.000	-1.68	5.97
	Mixed Dementia	-1.964	1.360	1.000	-6.33	2.40
	VaD	-1.472	1.906	1.000	-7.59	4.65
	unspecified dementia	4.432	1.774	.457	-1.26	10.13
	other dementia	8.199	3.067	.277	-1.65	18.05
	other psychiatric disorder	10.057*	1.293	.000	5.91	14.21
MCI	diagnosis not listed	8.259*	1.290	.000	4.12	12.40
	no diagnosis	1.316	2.143	1.000	-5.56	8.19
	AD	-2.144	1.192	1.000	-5.97	1.68
	Mixed Dementia	-4.108	1.557	.307	-9.11	.89
	VaD	-3.616	2.051	1.000	-10.20	2.97
	unspecified dementia	2.289	1.929	1.000	-3.90	8.48
	other dementia	6.056	3.159	1.000	-4.09	16.20
	other psychiatric disorder	7.914*	1.499	.000	3.10	12.73
Mixed Dementia	diagnosis not listed	12.367*	1.446	.000	7.72	17.01
	no diagnosis	5.423	2.240	.567	-1.77	12.62
	AD	1.964	1.360	1.000	-2.40	6.33
	MCI	4.108	1.557	.307	-.89	9.11
	VaD	.492	2.153	1.000	-6.42	7.40
	unspecified dementia	6.397	2.037	.063	-.14	12.94
	other dementia	10.163	3.226	.061	-.19	20.52
	other psychiatric disorder	12.022*	1.635	.000	6.77	17.27
VaD	diagnosis not listed	11.875*	1.968	.000	5.56	18.19
	no diagnosis	4.931	2.608	1.000	-3.44	13.30
	AD	1.472	1.906	1.000	-4.65	7.59
	MCI	3.616	2.051	1.000	-2.97	10.20
	Mixed Dementia	-.492	2.153	1.000	-7.40	6.42

	unspecified dementia	5.905	2.435	.561	-1.91	13.72
	other dementia	9.671	3.492	.208	-1.54	20.88
	other psychiatric disorder	11.530*	2.111	.000	4.75	18.31
unspecified dementia	diagnosis not listed	5.970*	1.841	.045	.06	11.88
	no diagnosis	-.973	2.513	1.000	-9.04	7.09
	AD	-4.432	1.774	.457	-10.13	1.26
	MCI	-2.289	1.929	1.000	-8.48	3.90
	Mixed Dementia	-6.397	2.037	.063	-12.94	.14
	VaD	-5.905	2.435	.561	-13.72	1.91
	other dementia	3.767	3.421	1.000	-7.22	14.75
	other psychiatric disorder	5.625	1.992	.176	-.77	12.02
other dementia	diagnosis not listed	2.204	3.106	1.000	-7.77	12.18
	no diagnosis	-4.740	3.546	1.000	-16.13	6.65
	AD	-8.199	3.067	.277	-18.05	1.65
	MCI	-6.056	3.159	1.000	-16.20	4.09
	Mixed Dementia	-10.163	3.226	.061	-20.52	.19
	VaD	-9.671	3.492	.208	-20.88	1.54
	unspecified dementia	-3.767	3.421	1.000	-14.75	7.22
	other psychiatric disorder	1.858	3.199	1.000	-8.41	12.13
other psychiatric disorder	diagnosis not listed	.345	1.383	1.000	-4.10	4.79
	no diagnosis	-6.598	2.200	.101	-13.66	.47
	AD	-10.057*	1.293	.000	-14.21	-5.91
	MCI	-7.914*	1.499	.000	-12.73	-3.10
	Mixed Dementia	-12.022*	1.635	.000	-17.27	-6.77
	VaD	-11.530*	2.111	.000	-18.31	-4.75
	unspecified dementia	-5.625	1.992	.176	-12.02	.77
	other dementia	-1.858	3.199	1.000	-12.13	8.41

APPENDIX 3

Chapter 5: Group differences (between diagnostic categories) in age, average MMSE, WMH load, normalised hippocampal volume and ypred score in the portion of the BRC memory clinic cohort used in the chapter 5 study, as measured by ANOVA and Bonferroni's post-hoc tests. $P < 0.05$ is considered statistically significant.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
age	Between Groups	4315.356	8	539.420	5.779	.000
	Within Groups	54136.471	580	93.339		
	Total	58451.827	588			
MMSE	Between Groups	1979.175	8	247.397	12.189	.000
	Within Groups	8504.087	419	20.296		
	Total	10483.262	427			
ypred - uncorrected	Between Groups	10.891	8	1.361	11.075	.000
	Within Groups	71.297	580	.123		
	Total	82.188	588			
normalise HC volume	Between Groups	.000	8	.000	7.393	.000
	Within Groups	.000	580	.000		
	Total	.000	588			
WMH load (mL)	Between Groups	5102.861	8	637.858	4.082	.000
	Within Groups	90626.646	580	156.253		
	Total	95729.506	588			

Multiple Comparisons

Bonferroni

Dependent Variable	(I) Diagnosis Category	(J) Diagnosis Category	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
age	diagnosis not listed	no diagnosis	-1.715	2.747	1.000	-10.54	7.11
		AD	-4.711*	1.007	.000	-7.95	-1.48
		MCI	-3.039	1.482	1.000	-7.80	1.72
		Mixed Dementia	-6.308*	1.680	.007	-11.70	-.91
		VaD	-4.647	2.420	1.000	-12.42	3.13
		unspecified dementia	-2.367	2.193	1.000	-9.41	4.68
		other dementia	2.824	3.469	1.000	-8.32	13.97
		other psychiatric	3.324	1.609	1.000	-1.84	8.49
	no diagnosis	diagnosis not listed	1.715	2.747	1.000	-7.11	10.54
		AD	-2.996	2.798	1.000	-11.98	5.99
		MCI	-1.324	3.002	1.000	-10.97	8.32
		Mixed Dementia	-4.593	3.104	1.000	-14.57	5.38
		VaD	-2.932	3.560	1.000	-14.37	8.50
		unspecified dementia	-.652	3.409	1.000	-11.60	10.30
		other dementia	4.538	4.341	1.000	-9.41	18.48

	other psychiatric	5.038	3.066	1.000	-4.81	14.89
AD	diagnosis not listed	4.711*	1.007	.000	1.48	7.95
	no diagnosis	2.996	2.798	1.000	-5.99	11.98
	MCI	1.672	1.574	1.000	-3.39	6.73
	Mixed Dementia	-1.597	1.762	1.000	-7.26	4.06
	VaD	.064	2.478	1.000	-7.90	8.02
	unspecified dementia	2.344	2.257	1.000	-4.91	9.59
	other dementia	7.535	3.509	1.000	-3.74	18.81
	other psychiatric	8.035*	1.694	.000	2.59	13.48
MCI	diagnosis not listed	3.039	1.482	1.000	-1.72	7.80
	no diagnosis	1.324	3.002	1.000	-8.32	10.97
	AD	-1.672	1.574	1.000	-6.73	3.39
	Mixed Dementia	-3.269	2.070	1.000	-9.92	3.38
	VaD	-1.608	2.706	1.000	-10.30	7.08
	unspecified dementia	.672	2.505	1.000	-7.37	8.72
	other dementia	5.863	3.674	1.000	-5.94	17.67

	other psychiatric	6.363	2.013	.060	-.10	12.83
Mixed Dementia	diagnosis not listed	6.308*	1.680	.007	.91	11.70
	no diagnosis	4.593	3.104	1.000	-5.38	14.57
	AD	1.597	1.762	1.000	-4.06	7.26
	MCI	3.269	2.070	1.000	-3.38	9.92
	VaD	1.661	2.819	1.000	-7.40	10.72
	unspecified dementia	3.941	2.627	1.000	-4.50	12.38
	other dementia	9.132	3.758	.555	-2.94	21.20
	other psychiatric	9.632*	2.163	.000	2.68	16.58
VaD	diagnosis not listed	4.647	2.420	1.000	-3.13	12.42
	no diagnosis	2.932	3.560	1.000	-8.50	14.37
	AD	-.064	2.478	1.000	-8.02	7.90
	MCI	1.608	2.706	1.000	-7.08	10.30
	Mixed Dementia	-1.661	2.819	1.000	-10.72	7.40
	unspecified dementia	2.280	3.152	1.000	-7.85	12.41
	other dementia	7.471	4.142	1.000	-5.84	20.78

	other psychiatric	7.971	2.777	.153	-.95	16.89
unspecified dementia	diagnosis not listed	2.367	2.193	1.000	-4.68	9.41
	no diagnosis	.652	3.409	1.000	-10.30	11.60
	AD	-2.344	2.257	1.000	-9.59	4.91
	MCI	-.672	2.505	1.000	-8.72	7.37
	Mixed Dementia	-3.941	2.627	1.000	-12.38	4.50
	VaD	-2.280	3.152	1.000	-12.41	7.85
	other dementia	5.190	4.014	1.000	-7.70	18.09
	other psychiatric	5.690	2.582	1.000	-2.60	13.99
other dementia	diagnosis not listed	-2.824	3.469	1.000	-13.97	8.32
	no diagnosis	-4.538	4.341	1.000	-18.48	9.41
	AD	-7.535	3.509	1.000	-18.81	3.74
	MCI	-5.863	3.674	1.000	-17.67	5.94
	Mixed Dementia	-9.132	3.758	.555	-21.20	2.94
	VaD	-7.471	4.142	1.000	-20.78	5.84
	unspecified dementia	-5.190	4.014	1.000	-18.09	7.70
	other psychiatric	.500	3.727	1.000	-11.47	12.47

	other psychiatric	diagnosis not listed	-3.324	1.609	1.000	-8.49	1.84
		no diagnosis	-5.038	3.066	1.000	-14.89	4.81
		AD	-8.035*	1.694	.000	-13.48	-2.59
		MCI	-6.363	2.013	.060	-12.83	.10
		Mixed Dementia	-9.632*	2.163	.000	-16.58	-2.68
		VaD	-7.971	2.777	.153	-16.89	.95
		unspecified dementia	-5.690	2.582	1.000	-13.99	2.60
		other dementia	-.500	3.727	1.000	-12.47	11.47
MMSE	diagnosis not listed	no diagnosis	-.579	1.333	1.000	-4.87	3.71
		AD	3.814*	.597	.000	1.89	5.74
		MCI	-.705	.784	1.000	-3.23	1.82
		Mixed Dementia	3.857*	.866	.000	1.07	6.64
		VaD	5.118*	1.187	.001	1.30	8.94
		unspecified dementia	5.216*	1.087	.000	1.72	8.72
		other dementia	6.883*	1.659	.001	1.54	12.22
		other psychiatric	1.812	.836	1.000	-.88	4.50
	no diagnosis	diagnosis not listed	.579	1.333	1.000	-3.71	4.87
		AD	4.392*	1.305	.030	.19	8.59
		MCI	-.127	1.400	1.000	-4.63	4.38
		Mixed Dementia	4.435	1.448	.084	-.22	9.09
		VaD	5.697*	1.660	.024	.35	11.04

	unspecified dementia	5.795*	1.590	.011	.68	10.91
	other dementia	7.462*	2.024	.009	.95	13.98
	other psychiatric	2.390	1.430	1.000	-2.21	6.99
AD	diagnosis not listed	-3.814*	.597	.000	-5.74	-1.89
	no diagnosis	-4.392*	1.305	.030	-8.59	-.19
	MCI	-4.519*	.734	.000	-6.88	-2.16
	Mixed Dementia	.043	.822	1.000	-2.60	2.69
	VaD	1.305	1.155	1.000	-2.41	5.02
	unspecified dementia	1.403	1.052	1.000	-1.98	4.79
	other dementia	3.069	1.636	1.000	-2.20	8.34
	other psychiatric	-2.002	.790	.419	-4.54	.54
MCI	diagnosis not listed	.705	.784	1.000	-1.82	3.23
	no diagnosis	.127	1.400	1.000	-4.38	4.63
	AD	4.519*	.734	.000	2.16	6.88
	Mixed Dementia	4.562*	.965	.000	1.45	7.67
	VaD	5.824*	1.262	.000	1.76	9.88
	unspecified dementia	5.922*	1.168	.000	2.16	9.68
	other dementia	7.588*	1.713	.000	2.07	13.10

	other psychiatric	2.517	.939	.275	-.50	5.54
Mixed Dementia	diagnosis not listed	-3.857*	.866	.000	-6.64	-1.07
	no diagnosis	-4.435	1.448	.084	-9.09	.22
	AD	-.043	.822	1.000	-2.69	2.60
	MCI	-4.562*	.965	.000	-7.67	-1.45
	VaD	1.262	1.315	1.000	-2.97	5.49
	unspecified dementia	1.360	1.225	1.000	-2.58	5.30
	other dementia	3.026	1.752	1.000	-2.61	8.67
	other psychiatric	-2.045	1.009	1.000	-5.29	1.20
VaD	diagnosis not listed	-5.118*	1.187	.001	-8.94	-1.30
	no diagnosis	-5.697*	1.660	.024	-11.04	-.35
	AD	-1.305	1.155	1.000	-5.02	2.41
	MCI	-5.824*	1.262	.000	-9.88	-1.76
	Mixed Dementia	-1.262	1.315	1.000	-5.49	2.97
	unspecified dementia	.098	1.470	1.000	-4.63	4.83
	other dementia	1.765	1.932	1.000	-4.45	7.98
	other psychiatric	-3.307	1.295	.397	-7.47	.86
	diagnosis not listed	-5.216*	1.087	.000	-8.72	-1.72

	unspecified dementia	no diagnosis	-5.795*	1.590	.011	-10.91	-.68
		AD	-1.403	1.052	1.000	-4.79	1.98
		MCI	-5.922*	1.168	.000	-9.68	-2.16
		Mixed Dementia	-1.360	1.225	1.000	-5.30	2.58
		VaD	-.098	1.470	1.000	-4.83	4.63
		other dementia	1.667	1.872	1.000	-4.36	7.69
		other psychiatric	-3.405	1.204	.177	-7.28	.47
	other dementia	diagnosis not listed	-6.883*	1.659	.001	-12.22	-1.54
		no diagnosis	-7.462*	2.024	.009	-13.98	-.95
		AD	-3.069	1.636	1.000	-8.34	2.20
		MCI	-7.588*	1.713	.000	-13.10	-2.07
		Mixed Dementia	-3.026	1.752	1.000	-8.67	2.61
		VaD	-1.765	1.932	1.000	-7.98	4.45
		unspecified dementia	-1.667	1.872	1.000	-7.69	4.36
		other psychiatric	-5.071	1.738	.134	-10.66	.52
	other psychiatric	diagnosis not listed	-1.812	.836	1.000	-4.50	.88
		no diagnosis	-2.390	1.430	1.000	-6.99	2.21
		AD	2.002	.790	.419	-.54	4.54
		MCI	-2.517	.939	.275	-5.54	.50
		Mixed Dementia	2.045	1.009	1.000	-1.20	5.29

		VaD	3.307	1.295	.397	-.86	7.47
		unspecified dementia	3.405	1.204	.177	-.47	7.28
		other dementia	5.071	1.738	.134	-.52	10.66
ypred - uncorrected	diagnosis not listed	no diagnosis	-.179007599	.09968908490	1.000	-.4992568340	.1412416360
		AD	-.28162770500*	.03654745080	.000	-.3990356760	-.1642197350
		MCI	.04512271250	.05378083170	1.000	-.1276471570	.2178925820
		Mixed Dementia	-.28238343900*	.06096687020	.000	-.4782383160	-.0865285611
		VaD	-.01708482080	.08782373030	1.000	-.2992168360	.2650471950
		unspecified dementia	-.15296569100	.07959701520	1.000	-.4086695450	.1027381630
		other dementia	.03380495860	.12588812600	1.000	-.3706081840	.4382181010
		other psychiatric	.04814223030	.05838556240	1.000	-.1394202470	.2357047070
	no diagnosis	diagnosis not listed	.17900759900	.09968908490	1.000	-.1412416360	.4992568340
		AD	-.10262010600	.10153572700	1.000	-.4288016430	.2235614300
		MCI	.22413031200	.10893193100	1.000	-.1258113850	.5740720080
		Mixed Dementia	-.10337584000	.11265321500	1.000	-.4652720900	.2585204110
		VaD	.16192277800	.12917737900	1.000	-.2530570250	.5769025820
		unspecified dementia	.02604190770	.12373145300	1.000	-.3714429650	.4235267810
		other dementia	.21281255800	.15754874800	1.000	-.2933097130	.7189348290

	other psychiatric	.22714982900	.11127740800	1.000	-.1303266680	.5846263260
AD	diagnosis not listed	.28162770500*	.03654745080	.000	.1642197350	.3990356760
	no diagnosis	.10262010600	.10153572700	1.000	-.2235614300	.4288016430
	MCI	.32675041800*	.05713114790	.000	.1432177230	.5102831130
	Mixed Dementia	-.00075573348	.06394176620	1.000	-.2061674070	.2046559400
	VaD	.26454288400	.08991439160	.122	-.0243053395	.5533911080
	unspecified dementia	.12866201400	.08189795500	1.000	-.1344335640	.3917575920
	other dementia	.31543266400	.12735545000	.487	-.0936942262	.7245595540
	other psychiatric	.32976993600*	.06148547890	.000	.1322490380	.5272908330
MCI	diagnosis not listed	-.04512271250	.05378083170	1.000	-.2178925820	.1276471570
	no diagnosis	-.22413031200	.10893193100	1.000	-.5740720080	.1258113850
	AD	-.32675041800*	.05713114790	.000	-.5102831130	-.1432177230
	Mixed Dementia	-.32750615100*	.07513462030	.001	-.5688746490	-.0861376537
	VaD	-.06220753330	.09818991550	1.000	-.3776407160	.2532256490
	unspecified dementia	-.19808840400	.09090619740	1.000	-.4901227850	.0939459767
	other dementia	-.01131775390	.13332693700	1.000	-.4396279320	.4169924240
	other psychiatric	.00301951775	.07305563500	1.000	-.2316702800	.2377093160
Mixed Dementia	diagnosis not listed	.28238343900*	.06096687020	.000	.0865285611	.4782383160

	no diagnosis	.10337584000	.11265321500	1.000	-.2585204110	.4652720900
	AD	.00075573348	.06394176620	1.000	-.2046559400	.2061674070
	MCI	.32750615100*	.07513462030	.001	.0861376537	.5688746490
	VaD	.26529861800	.10230269300	.351	-.0633467806	.5939440170
	unspecified dementia	.12941774700	.09533371980	1.000	-.1768399620	.4356754570
	other dementia	.31618839700	.13638421300	.748	-.1219432200	.7543200140
	other psychiatric	.33052566900*	.07849654270	.001	.0783570615	.5826942770
VaD	diagnosis not listed	.01708482080	.08782373030	1.000	-.2650471950	.2992168360
	no diagnosis	-.16192277800	.12917737900	1.000	-.5769025820	.2530570250
	AD	-.26454288400	.08991439160	.122	-.5533911080	.0243053395
	MCI	.06220753330	.09818991550	1.000	-.2532256490	.3776407160
	Mixed Dementia	-.26529861800	.10230269300	.351	-.5939440170	.0633467806
	unspecified dementia	-.13588087100	.11438779000	1.000	-.5033494080	.2315876670
	other dementia	.05088977940	.15032199400	1.000	-.4320166860	.5337962450
	other psychiatric	.06522705110	.10078569100	1.000	-.2585450100	.3889991120
unspecified dementia	diagnosis not listed	.15296569100	.07959701520	1.000	-.1027381630	.4086695450
	no diagnosis	-.02604190770	.12373145300	1.000	-.4235267810	.3714429650
	AD	-.12866201400	.08189795500	1.000	-.3917575920	.1344335640
	MCI	.19808840400	.09090619740	1.000	-.0939459767	.4901227850

	Mixed Dementia	-.12941774700	.09533371980	1.000	-.4356754570	.1768399620
	VaD	.13588087100	.11438779000	1.000	-.2315876670	.5033494080
	other dementia	.18677065000	.14566873100	1.000	-.2811872980	.6547285980
	other psychiatric	.20110792200	.09370396350	1.000	-.0999142277	.5021300710
other dementia	diagnosis not listed	-.03380495860	.12588812600	1.000	-.4382181010	.3706081840
	no diagnosis	-.21281255800	.15754874800	1.000	-.7189348290	.2933097130
	AD	-.31543266400	.12735545000	.487	-.7245595540	.0936942262
	MCI	.01131775390	.13332693700	1.000	-.4169924240	.4396279320
	Mixed Dementia	-.31618839700	.13638421300	.748	-.7543200140	.1219432200
	VaD	-.05088977940	.15032199400	1.000	-.5337962450	.4320166860
	unspecified dementia	-.18677065000	.14566873100	1.000	-.6547285980	.2811872980
	other psychiatric	.01433727170	.13525002100	1.000	-.4201507760	.4488253190
other psychiatric	diagnosis not listed	-.04814223030	.05838556240	1.000	-.2357047070	.1394202470
	no diagnosis	-.22714982900	.11127740800	1.000	-.5846263260	.1303266680
	AD	-.32976993600*	.06148547890	.000	-.5272908330	-.1322490380
	MCI	-.00301951775	.07305563500	1.000	-.2377093160	.2316702800
	Mixed Dementia	-.33052566900*	.07849654270	.001	-.5826942770	-.0783570615
	VaD	-.06522705110	.10078569100	1.000	-.3889991120	.2585450100

		unspecified dementia	-.20110792200	.09370396350	1.000	-.5021300710	.0999142277
		other dementia	-.01433727170	.13525002100	1.000	-.4488253190	.4201507760
normalise HC volume	diagnosis not listed	no diagnosis	.000233592642000	.000118827056000	1.000	-.000148136952000	.000615322236000
		AD	.000276498213000*	.000043563706100	.000	.000136550659000	.000416445766000
		MCI	.000007824580390	.000064105492800	1.000	-.000198113061000	.000213762222000
		Mixed Dementia	.000276850375000*	.000072671082600	.006	.000043395944010	.000510304806000
		VaD	.000087147972500	.000104683831000	1.000	-.000249146788000	.000423442733000
		unspecified dementia	.000143525463000	.000094877779400	1.000	-.000161267547000	.000448318473000
		other dementia	-.000015786328900	.000150055701000	1.000	-.000497837331000	.000466264673000
		other psychiatric	-.000077081108700	.000069594224100	1.000	-.000300651192000	.000146488975000
	no diagnosis	diagnosis not listed	-.000233592642000	.000118827056000	1.000	-.000615322236000	.000148136952000
		AD	.000042905570500	.000121028211000	1.000	-.000345895188000	.000431706329000
		MCI	-.000225768062000	.000129844312000	1.000	-.000642890375000	.000191354251000
		Mixed Dementia	.000043257732800	.000134279997000	1.000	-.000388114129000	.000474629595000

	VaD	-.000146444670000	.000153976413000	1.000	-.00064109088500	.00034820154500
	unspecified dementia	-.000090067179500	.000147484997000	1.000	-.00056385984600	.00038372548700
	other dementia	-.000249378971000	.000187794421000	1.000	-.00085266487400	.00035390693200
	other psychiatric	-.000310673751000	.000132640067000	.702	-.00073677737000	.00011542986800
AD	diagnosis not listed	-.000276498213000*	.000043563706100	.000	-.00041644576600	-.00013655065900
	no diagnosis	-.000042905570500	.000121028211000	1.000	-.00043170632900	.00034589518800
	MCI	-.000268673632000*	.000068098991400	.003	-.00048744031000	-.00004990695480
	Mixed Dementia	.000000352162281	.000076217089100	1.000	-.00024449374500	.00024519807000
	VaD	-.000189350240000	.000107175851000	1.000	-.00053365056400	.00015495008300
	unspecified dementia	-.000132972750000	.000097620445900	1.000	-.00044657652200	.00018063102200
	other dementia	-.000292284542000	.000151804716000	1.000	-.00077995422100	.00019538513700
	other psychiatric	-.000353579321000*	.000073289252000	.000	-.00058901960900	-.00011813903300
MCI	diagnosis not listed	-.000007824580390	.000064105492800	1.000	-.00021376222200	.00019811306100

	no diagnosis	.000225768062000	.000129844312000	1.000	-.000191354251000	.000642890375000
	AD	.000268673632000*	.000068098991400	.003	.000049906954800	.000487440310000
	Mixed Dementia	.000269025795000	.000089558709100	.100	-.000018679806300	.000556731396000
	VaD	.000079323392200	.000117040082000	1.000	-.000296665580000	.000455312364000
	unspecified dementia	.000135700882000	.000108358060000	1.000	-.000212397265000	.000483799030000
	other dementia	-.000023610909300	.000158922589000	1.000	-.000534146618000	.000486924800000
	other psychiatric	-.000084905689100	.000087080607300	1.000	-.000364650436000	.000194839058000
Mixed Dementia	diagnosis not listed	-.000276850375000*	.000072671082600	.006	-.000510304806000	-.000043395944010
	no diagnosis	-.000043257732800	.000134279997000	1.000	-.000474629595000	.000388114129000
	AD	-.000000352162281	.000076217089100	1.000	-.000245198070000	.000244493745000
	MCI	-.000269025795000	.000089558709100	.100	-.000556731396000	.000018679806300
	VaD	-.000189702402000	.000121942416000	1.000	-.000581440027000	.000202035222000
	unspecified dementia	-.000133324912000	.000113635563000	1.000	-.000498376935000	.000231727111000

	other dementia	-.000292636704000	.000162566791000	1.000	-.000814879339000	.000229605931000
	other psychiatric	-.000353931484000*	.000093566041900	.006	-.000654510563000	-.000053352404600
VaD	diagnosis not listed	-.000087147972500	.000104683831000	1.000	-.000423442733000	.000249146788000
	no diagnosis	.000146444670000	.000153976413000	1.000	-.000348201545000	.000641090885000
	AD	.000189350240000	.000107175851000	1.000	-.000154950083000	.000533650564000
	MCI	-.000079323392200	.000117040082000	1.000	-.000455312364000	.000296665580000
	Mixed Dementia	.000189702402000	.000121942416000	1.000	-.000202035222000	.000581440027000
	unspecified dementia	.000056377490200	.000136347569000	1.000	-.000381636407000	.000494391387000
	other dementia	-.000102934301000	.000179180300000	1.000	-.000678547508000	.000472678905000
	other psychiatric	-.000164229081000	.000120134185000	1.000	-.000550157802000	.000221699639000
unspecified dementia	diagnosis not listed	-.000143525463000	.000094877779400	1.000	-.000448318473000	.000161267547000
	no diagnosis	.000090067179500	.000147484997000	1.000	-.000383725487000	.000563859846000
	AD	.000132972750000	.000097620445900	1.000	-.000180631022000	.000446576522000

	MCI	-.000135700882000	.000108358060000	1.000	-.000483799030000	.000212397265000
	Mixed Dementia	.000133324912000	.000113635563000	1.000	-.000231727111000	.000498376935000
	VaD	-.000056377490200	.000136347569000	1.000	-.000494391387000	.000381636407000
	other dementia	-.000159311792000	.000173633719000	1.000	-.000717106716000	.000398483132000
	other psychiatric	-.000220606571000	.000111692932000	1.000	-.000579417929000	.000138204786000
other dementia	diagnosis not listed	.000015786328900	.000150055701000	1.000	-.000466264673000	.000497837331000
	no diagnosis	.000249378971000	.000187794421000	1.000	-.000353906932000	.000852664874000
	AD	.000292284542000	.000151804716000	1.000	-.000195385137000	.000779954221000
	MCI	.000023610909300	.000158922589000	1.000	-.000486924800000	.000534146618000
	Mixed Dementia	.000292636704000	.000162566791000	1.000	-.000229605931000	.000814879339000
	VaD	.000102934301000	.000179180300000	1.000	-.000472678905000	.000678547508000
	unspecified dementia	.000159311792000	.000173633719000	1.000	-.000398483132000	.000717106716000
	other psychiatric	-.000061294779800	.000161214860000	1.000	-.000579194365000	.000456604805000

	other psychiatric	diagnosis not listed	.000077081108700	.000069594224100	1.000	-.000146488975000	.000300651192000
		no diagnosis	.000310673751000	.000132640067000	.702	-.000115429868000	.000736777370000
		AD	.000353579321000*	.000073289252000	.000	.000118139033000	.000589019609000
		MCI	.000084905689100	.000087080607300	1.000	-.000194839058000	.000364650436000
		Mixed Dementia	.000353931484000*	.000093566041900	.006	.000053352404600	.000654510563000
		VaD	.000164229081000	.000120134185000	1.000	-.000221699639000	.000550157802000
		unspecified dementia	.000220606571000	.000111692932000	1.000	-.000138204786000	.000579417929000
		other dementia	.000061294779800	.000161214860000	1.000	-.000456604805000	.000579194365000
WMH load (mL)	diagnosis not listed	no diagnosis	-4.1227135	3.5541814	1.000	-15.540452	7.295025
		AD	-1.4019602	1.3030140	1.000	-5.587867	2.783947
		MCI	-.3357344	1.9174299	1.000	-6.495440	5.823972
		Mixed Dementia	-7.3172240*	2.1736313	.029	-14.299972	-.334476
		VaD	-14.7275539*	3.1311499	.000	-24.786312	-4.668796
		unspecified dementia	-1.5259199	2.8378456	1.000	-10.642443	7.590604
		other dementia	-.1200213	4.4882470	1.000	-14.538427	14.298384
		other psychiatric	.0266461	2.0816008	1.000	-6.660456	6.713748

no diagnosis	diagnosis not listed	4.1227135	3.5541814	1.000	-7.295025	15.540452
	AD	2.7207532	3.6200191	1.000	-8.908487	14.349994
	MCI	3.7869791	3.8837134	1.000	-8.689374	16.263333
	Mixed Dementia	-3.1945105	4.0163872	1.000	-16.097076	9.708055
	VaD	-10.6048404	4.6055176	.779	-25.399976	4.190295
	unspecified dementia	2.5967936	4.4113558	1.000	-11.574601	16.768188
	other dementia	4.0026922	5.6170325	1.000	-14.041915	22.047299
	other psychiatric	4.1493596	3.9673360	1.000	-8.595630	16.894349
AD	diagnosis not listed	1.4019602	1.3030140	1.000	-2.783947	5.587867
	no diagnosis	-2.7207532	3.6200191	1.000	-14.349994	8.908487
	MCI	1.0662258	2.0368776	1.000	-5.477204	7.609655
	Mixed Dementia	-5.9152637	2.2796943	.349	-13.238737	1.408209
	VaD	-13.3255936*	3.2056875	.001	-23.623802	-3.027385
	unspecified dementia	-.1239596	2.9198802	1.000	-9.504018	9.256098
	other dementia	1.2819390	4.5405610	1.000	-13.304524	15.868402
	other psychiatric	1.4286063	2.1921211	1.000	-5.613540	8.470752
MCI	diagnosis not listed	.3357344	1.9174299	1.000	-5.823972	6.495440
	no diagnosis	-3.7869791	3.8837134	1.000	-16.263333	8.689374

	AD	-1.0662258	2.0368776	1.000	-7.609655	5.477204
	Mixed Dementia	-6.9814896	2.6787493	.338	-15.586919	1.623940
	VaD	-14.3918195*	3.5007320	.002	-25.637852	-3.145786
	unspecified dementia	-1.1901855	3.2410480	1.000	-11.601989	9.221618
	other dementia	.2157131	4.7534604	1.000	-15.054685	15.486112
	other psychiatric	.3623805	2.6046280	1.000	-8.004936	8.729697
Mixed Dementia	diagnosis not listed	7.3172240*	2.1736313	.029	.334476	14.299972
	no diagnosis	3.1945105	4.0163872	1.000	-9.708055	16.097076
	AD	5.9152637	2.2796943	.349	-1.408209	13.238737
	MCI	6.9814896	2.6787493	.338	-1.623940	15.586919
	VaD	-7.4103299	3.6473634	1.000	-19.127414	4.306754
	unspecified dementia	5.7913041	3.3989010	1.000	-5.127599	16.710207
	other dementia	7.1972027	4.8624604	1.000	-8.423356	22.817762
	other psychiatric	7.3438700	2.7986108	.321	-1.646612	16.334352
VaD	diagnosis not listed	14.7275539*	3.1311499	.000	4.668796	24.786312
	no diagnosis	10.6048404	4.6055176	.779	-4.190295	25.399976
	AD	13.3255936*	3.2056875	.001	3.027385	23.623802
	MCI	14.3918195*	3.5007320	.002	3.145786	25.637852
	Mixed Dementia	7.4103299	3.6473634	1.000	-4.306754	19.127414

	unspecified dementia	13.2016340*	4.0782294	.046	.100402	26.302866
	other dementia	14.6075326	5.3593794	.238	-2.609369	31.824434
	other psychiatric	14.7541999*	3.5932783	.002	3.210864	26.297536
unspecified dementia	diagnosis not listed	1.5259199	2.8378456	1.000	-7.590604	10.642443
	no diagnosis	-2.5967936	4.4113558	1.000	-16.768188	11.574601
	AD	.1239596	2.9198802	1.000	-9.256098	9.504018
	MCI	1.1901855	3.2410480	1.000	-9.221618	11.601989
	Mixed Dementia	-5.7913041	3.3989010	1.000	-16.710207	5.127599
	VaD	-13.2016340*	4.0782294	.046	-26.302866	-.100402
	other dementia	1.4058986	5.1934782	1.000	-15.278049	18.089846
	other psychiatric	1.5525660	3.3407959	1.000	-9.179675	12.284807
other dementia	diagnosis not listed	.1200213	4.4882470	1.000	-14.298384	14.538427
	no diagnosis	-4.0026922	5.6170325	1.000	-22.047299	14.041915
	AD	-1.2819390	4.5405610	1.000	-15.868402	13.304524
	MCI	-.2157131	4.7534604	1.000	-15.486112	15.054685
	Mixed Dementia	-7.1972027	4.8624604	1.000	-22.817762	8.423356
	VaD	-14.6075326	5.3593794	.238	-31.824434	2.609369
	unspecified dementia	-1.4058986	5.1934782	1.000	-18.089846	15.278049

	other psychiatric	.1466673	4.8220235	1.000	-15.343989	15.637323
other psychiatric	diagnosis not listed	-.0266461	2.0816008	1.000	-6.713748	6.660456
	no diagnosis	-4.1493596	3.9673360	1.000	-16.894349	8.595630
	AD	-1.4286063	2.1921211	1.000	-8.470752	5.613540
	MCI	-.3623805	2.6046280	1.000	-8.729697	8.004936
	Mixed Dementia	-7.3438700	2.7986108	.321	-16.334352	1.646612
	VaD	-14.7541999*	3.5932783	.002	-26.297536	-3.210864
	unspecified dementia	-1.5525660	3.3407959	1.000	-12.284807	9.179675
	other dementia	-.1466673	4.8220235	1.000	-15.637323	15.343989

APPENDIX 4

Chapter 5: Group differences (between categories created using the median value of normalised hippocampal volume and WHM load) in age, average MMSE, WMH load, normalised hippocampal volume and ypred score in the portion of the BRC memory clinic cohort used in the chapter 5 study, as measured by ANOVA and Bonferroni's post-hoc tests. $P < 0.05$ is considered statistically significant.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
age	Between Groups	20076.619	3	6692.206	102.017	.000
	Within Groups	38375.208	585	65.599		
	Total	58451.827	588			
MMSE	Between Groups	693.163	3	231.054	10.007	.000
	Within Groups	9790.098	424	23.090		
	Total	10483.262	427			
ypred - uncorrected	Between Groups	35.387	3	11.796	147.442	.000
	Within Groups	46.801	585	.080		
	Total	82.188	588			
normalise HC volume	Between Groups	.000	3	.000	420.227	.000
	Within Groups	.000	585	.000		
	Total	.000	588			
WMH load (mL)	Between Groups	43418.097	3	14472.699	161.849	.000
	Within Groups	52311.409	585	89.421		
	Total	95729.506	588			

Multiple Comparisons

Bonferroni

Dependent Variable	(I) group 2 groups	(J) group 2 groups	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
age	normal-like	AD-like	-9.045*	.996	.000	-11.68	-6.41
		MD-like	-13.585*	.820	.000	-15.76	-11.41
		VaD-like	-11.768*	1.000	.000	-14.41	-9.12
	AD-like	normal-like	9.045*	.996	.000	6.41	11.68
		MD-like	-4.540*	.996	.000	-7.18	-1.90
		VaD-like	-2.724	1.148	.108	-5.76	.32
	MD-like	normal-like	13.585*	.820	.000	11.41	15.76
		AD-like	4.540*	.996	.000	1.90	7.18
		VaD-like	1.816	1.000	.418	-.83	4.46
	VaD-like	normal-like	11.768*	1.000	.000	9.12	14.41
		AD-like	2.724	1.148	.108	-.32	5.76
		MD-like	-1.816	1.000	.418	-4.46	.83
MMSE	normal-like	AD-like	1.639	.694	.111	-.20	3.48
		MD-like	3.104*	.569	.000	1.60	4.61
		VaD-like	1.238	.697	.458	-.61	3.09
	AD-like	normal-like	-1.639	.694	.111	-3.48	.20

		MD-like	1.465	.696	.215	-.38	3.31
		VaD-like	-.401	.804	1.000	-2.53	1.73
	MD-like	normal-like	-3.104*	.569	.000	-4.61	-1.60
		AD-like	-1.465	.696	.215	-3.31	.38
		VaD-like	-1.866*	.699	.047	-3.72	-.01
	VaD-like	normal-like	-1.238	.697	.458	-3.09	.61
		AD-like	.401	.804	1.000	-1.73	2.53
		MD-like	1.866*	.699	.047	.01	3.72
ypred - uncorrected	normal-like	AD-like	-.51522883500*	.03478925470	.000	-.6073250720	-.4231325970
		MD-like	-.55349771700*	.02864501900	.000	-.6293285590	-.4776668750
		VaD-like	-.21576150000*	.03490520430	.000	-.3081646870	-.1233583140
	AD-like	normal-like	.51522883500*	.03478925470	.000	.4231325970	.6073250720
		MD-like	-.03826888190	.03478925470	1.000	-.1303651200	.0538273557
		VaD-like	.29946733500*	.04010147650	.000	.1933082590	.4056264100
	MD-like	normal-like	.55349771700*	.02864501900	.000	.4776668750	.6293285590
		AD-like	.03826888190	.03478925470	1.000	-.0538273557	.1303651200
		VaD-like	.33773621700*	.03490520430	.000	.2453330300	.4301394030
	VaD-like	normal-like	.21576150000*	.03490520430	.000	.1233583140	.3081646870
		AD-like	-.29946733500*	.04010147650	.000	-.4056264100	-.1933082590

		MD-like	-.33773621700*	.03490520430	.000	-.4301394030	-.2453330300
normalise HC volume	normal-like	AD-like	.000741051056000*	.000030248500700	.000	.000660975380000	.000821126733000
		MD-like	.000800469349000*	.000024906221300	.000	.000734536080000	.000866402617000
		VaD-like	.000235285339000*	.000030349316400	.000	.000154942777000	.000315627901000
	AD-like	normal-like	-.000741051056000*	.000030248500700	.000	-.000821126733000	-.000660975380000
		MD-like	.000059418292600	.000030248500700	.300	-.000020657383900	-.000139493969000
		VaD-like	-.000505765717000*	.000034867362100	.000	-.000598068725000	-.000413462709000
	MD-like	normal-like	-.000800469349000*	.000024906221300	.000	-.000866402617000	-.000734536080000
		AD-like	-.000059418292600	.000030248500700	.300	-.000139493969000	.000020657383900
		VaD-like	-.000565184010000*	.000030349316400	.000	-.000645526572000	-.000484841448000
	VaD-like	normal-like	-.000235285339000*	.000030349316400	.000	-.000315627901000	-.000154942777000
		AD-like	.000505765717000*	.000034867362100	.000	.000413462709000	.000598068725000
		MD-like	.000565184010000*	.000030349316400	.000	.000484841448000	.000645526572000
WMH load (mL)	normal-like	AD-like	-1.1988679	1.1630918	1.000	-4.277875	1.880140
		MD-like	-17.5413608*	.9576746	.000	-20.076575	-15.006146
		VaD-like	-17.5939451*	1.1669682	.000	-20.683215	-14.504676

	AD-like	normal-like	1.1988679	1.1630918	1.000	-1.880140	4.277875
		MD-like	-16.3424929*	1.1630918	.000	-19.421500	-13.263485
		VaD-like	-16.3950772*	1.3406926	.000	-19.944241	-12.845914
	MD-like	normal-like	17.5413608*	.9576746	.000	15.006146	20.076575
		AD-like	16.3424929*	1.1630918	.000	13.263485	19.421500
		VaD-like	-.0525843	1.1669682	1.000	-3.141854	3.036685
	VaD-like	normal-like	17.5939451*	1.1669682	.000	14.504676	20.683215
		AD-like	16.3950772*	1.3406926	.000	12.845914	19.944241
		MD-like	.0525843	1.1669682	1.000	-3.036685	3.141854

APPENDIX 5

Chapter 5: Group differences (between categories created using the median value of ypred score and WHM load) in age, average MMSE, WMH load, normalised hippocampal volume and ypred score in the portion of the BRC memory clinic cohort used in the chapter 5 study, as measured by ANOVA and Bonferroni's post-hoc tests. $P < 0.05$ is considered statistically significant.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
age	Between Groups	24963.333	3	8321.111	145.359	.000
	Within Groups	33488.494	585	57.245		
	Total	58451.827	588			
MMSE	Between Groups	1333.952	3	444.651	20.606	.000
	Within Groups	9149.310	424	21.579		
	Total	10483.262	427			
ypred - uncorrected	Between Groups	47.234	3	15.745	263.498	.000
	Within Groups	34.955	585	.060		
	Total	82.188	588			
normalise HC volume	Between Groups	.000	3	.000	145.198	.000
	Within Groups	.000	585	.000		
	Total	.000	588			
WMH load (mL)	Between Groups	43556.671	3	14518.890	162.796	.000
	Within Groups	52172.835	585	89.184		
	Total	95729.506	588			

Multiple Comparisons

Bonferroni

Dependent Variable	(I) group 2 groups with ypred	(J) group 2 groups with ypred	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
age	control like	AD like	-11.973*	.911	.000	-14.38	-9.56
		MD like	-17.887*	.858	.000	-20.16	-15.62
		VaD like	-12.934*	1.602	.000	-17.17	-8.69
	AD like	control like	11.973*	.911	.000	9.56	14.38
		MD like	-5.914*	.724	.000	-7.83	-4.00
		VaD like	-.961	1.534	1.000	-5.02	3.10
	MD like	control like	17.887*	.858	.000	15.62	20.16
		AD like	5.914*	.724	.000	4.00	7.83
		VaD like	4.953*	1.503	.006	.97	8.93
	VaD like	control like	12.934*	1.602	.000	8.69	17.17
		AD like	.961	1.534	1.000	-3.10	5.02
		MD like	-4.953*	1.503	.006	-8.93	-.97
MMSE	control like	AD like	2.943*	.656	.000	1.20	4.68
		MD like	4.349*	.623	.000	2.70	6.00
		VaD like	-.499	1.083	1.000	-3.37	2.37

	AD like	control like	-2.943*	.656	.000	-4.68	-1.20
		MD like	1.405*	.522	.044	.02	2.79
		VaD like	-3.442*	1.028	.005	-6.17	-.72
	MD like	control like	-4.349*	.623	.000	-6.00	-2.70
		AD like	-1.405*	.522	.044	-2.79	-.02
		VaD like	-4.848*	1.007	.000	-7.52	-2.18
	VaD like	control like	.499	1.083	1.000	-2.37	3.37
		AD like	3.442*	1.028	.005	.72	6.17
		MD like	4.848*	1.007	.000	2.18	7.52
ypred - uncorrected	control like	AD like	-.62708830100*	.02943099350	.000	-.7049998220	-.5491767790
		MD like	-.71747974900*	.02770976760	.000	-.7908347360	-.6441247610
		VaD like	-.09688133440	.05174165390	.370	-.2338549970	.0400923287
	AD like	control like	.62708830100*	.02943099350	.000	.5491767790	.7049998220
		MD like	-.09039144790*	.02340117750	.001	-.1523404730	-.0284424232
		VaD like	.53020696600*	.04956795980	.000	.3989876390	.6614262940
	MD like	control like	.71747974900*	.02770976760	.000	.6441247610	.7908347360
		AD like	.09039144790*	.02340117750	.001	.0284424232	.1523404730
		VaD like	.62059841400*	.04856573360	.000	.4920322410	.7491645870
	VaD like	control like	.09688133440	.05174165390	.370	-.0400923287	.2338549970

		AD like	-.53020696600*	.04956795980	.000	-.6614262940	-.3989876390
		MD like	-.62059841400*	.04856573360	.000	-.7491645870	-.4920322410
normalise HC volume	control like	AD like	.000589382228000*	.000039819034700	.000	.00048397085000	.00069479360600
		MD like	.000769620859000*	.000037490280300	.000	.00067037430200	.00086886741700
		VaD like	.000338493596000*	.000070004524700	.000	.00015317334700	.00052381384500
	AD like	control like	-.000589382228000*	.000039819034700	.000	-.00069479360600	-.00048397085000
		MD like	.000180238631000*	.000031660918900	.000	.00009642391540	.00026405334800
		VaD like	-.000250888632000*	.000067063597700	.001	-.00042842347900	-.00007335378410
	MD like	control like	-.000769620859000*	.000037490280300	.000	-.00086886741700	-.00067037430200
		AD like	-.000180238631000*	.000031660918900	.000	-.00026405334800	-.00009642391540
		VaD like	-.000431127263000*	.000065707623100	.000	-.00060507249200	-.00025718203400
	VaD like	control like	-.000338493596000*	.000070004524700	.000	-.00052381384500	-.00015317334700
		AD like	.000250888632000*	.000067063597700	.001	.00007335378410	.00042842347900
		MD like	.000431127263000*	.000065707623100	.000	.00025718203400	.00060507249200
WMH load (mL)	control like	AD like	-1.8361528	1.1370330	.641	-4.846176	1.173870
		MD like	-18.2835233*	1.0705354	.000	-21.117510	-15.449537

	VaD like	-18.5001821*	1.9989801	.000	-23.792004	-13.208360
AD like	control like	1.8361528	1.1370330	.641	-1.173870	4.846176
	MD like	-16.4473705*	.9040779	.000	-18.840701	-14.054040
	VaD like	-16.6640294*	1.9150019	.000	-21.733539	-11.594520
MD like	control like	18.2835233*	1.0705354	.000	15.449537	21.117510
	AD like	16.4473705*	.9040779	.000	14.054040	18.840701
	VaD like	-.2166588	1.8762820	1.000	-5.183667	4.750349
VaD like	control like	18.5001821*	1.9989801	.000	13.208360	23.792004
	AD like	16.6640294*	1.9150019	.000	11.594520	21.733539
	MD like	.2166588	1.8762820	1.000	-4.750349	5.183667

APPENDIX 6

Chapter 5: Group differences (between categories created using the 33rd percentile values of normalised hippocampal volume and WHM load) in age, average MMSE, WMH load, normalised hippocampal volume and ypred score in the portion of the BRC memory clinic cohort used in the chapter 5 study, as measured by ANOVA and Bonferroni's post-hoc tests. $P < 0.05$ is considered statistically significant.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
age	Between Groups	12637.284	3	4212.428	53.788	.000
	Within Groups	45814.542	585	78.315		
	Total	58451.827	588			
MMSE	Between Groups	741.782	3	247.261	10.762	.000
	Within Groups	9741.480	424	22.975		
	Total	10483.262	427			
ypred - uncorrected	Between Groups	30.550	3	10.183	115.367	.000
	Within Groups	51.638	585	.088		
	Total	82.188	588			
normalise HC volume	Between Groups	.000	3	.000	307.223	.000
	Within Groups	.000	585	.000		
	Total	.000	588			
WMH load (mL)	Between Groups	57678.221	3	19226.074	295.581	.000
	Within Groups	38051.286	585	65.045		
	Total	95729.506	588			

Multiple Comparisons

Bonferroni

Dependent Variable	(I) groups thirds	(J) groups thirds	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
age	Control-like	AD-like	-7.579*	1.035	.000	-10.32	-4.84
		MD-like	-10.404*	1.027	.000	-13.12	-7.68
		VaD-like	-9.342*	1.035	.000	-12.08	-6.60
	AD-like	Control-like	7.579*	1.035	.000	4.84	10.32
		MD-like	-2.825	1.264	.155	-6.17	.52
		VaD-like	-1.763	1.271	.995	-5.13	1.60
	MD-like	Control-like	10.404*	1.027	.000	7.68	13.12
		AD-like	2.825	1.264	.155	-.52	6.17
		VaD-like	1.062	1.264	1.000	-2.28	4.41
	VaD-like	Control-like	9.342*	1.035	.000	6.60	12.08
		AD-like	1.763	1.271	.995	-1.60	5.13
		MD-like	-1.062	1.264	1.000	-4.41	2.28
MMSE	Control-like	AD-like	1.853*	.661	.032	.10	3.61
		MD-like	3.213*	.650	.000	1.49	4.94
		VaD-like	2.446*	.672	.002	.66	4.23
	AD-like	Control-like	-1.853*	.661	.032	-3.61	-.10
		MD-like	1.359	.808	.558	-.78	3.50
		VaD-like	.593	.825	1.000	-1.59	2.78

	MD-like	Control-like	-3.213*	.650	.000	-4.94	-1.49
		AD-like	-1.359	.808	.558	-3.50	.78
		VaD-like	-.766	.817	1.000	-2.93	1.40
	VaD-like	Control-like	-2.446*	.672	.002	-4.23	-.66
		AD-like	-.593	.825	1.000	-2.78	1.59
		MD-like	.766	.817	1.000	-1.40	2.93
ypred - uncorrected	Control-like	AD-like	-.49538380700*	.03475933480	.000	-.5874008390	-.4033667750
		MD-like	-.52108651100*	.03449387610	.000	-.6124008050	-.4297722180
		VaD-like	-.17933970500*	.03475933480	.000	-.2713567370	-.0873226730
	AD-like	Control-like	.49538380700*	.03475933480	.000	.4033667750	.5874008390
		MD-like	-.02570270450	.04244548260	1.000	-.1380669760	.0866615666
		VaD-like	.31604410200*	.04266149150	.000	.2031079990	.4289802050
	MD-like	Control-like	.52108651100*	.03449387610	.000	.4297722180	.6124008050
		AD-like	.02570270450	.04244548260	1.000	-.0866615666	.1380669760
		VaD-like	.34174680700*	.04244548260	.000	.2293825350	.4541110780
	VaD-like	Control-like	.17933970500*	.03475933480	.000	.0873226730	.2713567370
		AD-like	-.31604410200*	.04266149150	.000	-.4289802050	-.2031079990
		MD-like	-.34174680700*	.04244548260	.000	-.4541110780	-.2293825350
normalise HC volume	Control-like	AD-like	.000730 41677300 0*	.000031 84520160 0	.000	.000647 11421200	.000815 71933300
		MD-like	.000784 49821400 0*	.000031 60199820 0	.000	.000700 83947600	.000868 15695200
		VaD-like	.000235 80779300 0*	.000031 84520160 0	.000	.000151 50523300	.000320 11035400

	AD-like	Control-like	-.00073141677300 0*	.00003184520160 0	.000	-.0008157193330 0	-.0006471142120 0
		MD-like	.00005308144150 0	.00003888696250 0	1.000	-.0000498624981 0	.0001560253810 0
		VaD-like	-.00049560897900 0*	.00003908486180 0	.000	-.0005990768100 0	-.0003921411490 0
	MD-like	Control-like	-.00078449821400 0*	.00003160199820 0	.000	-.0008681569520 0	-.0007008394760 0
		AD-like	-.00005308144150 0	.00003888696250 0	1.000	-.0001560253810 0	.0000498624981 0
		VaD-like	-.00054869042100 0*	.00003888696250 0	.000	-.0006516343610 0	-.0004457464810 0
	VaD-like	Control-like	-.00023580779300 0*	.00003184520160 0	.000	-.0003201103540 0	-.0001515052330 0
		AD-like	.00049560897900 0*	.00003908486180 0	.000	.0003921411490 0	.0005990768100 0
		MD-like	.00054869042100 0*	.00003888696250 0	.000	.0004457464810 0	.0006516343610 0
WMH load (mL)	Control-like	AD-like	-1.7023836	.9435638	.430	-4.200243	.795476
		MD-like	-21.4678453*	.9363578	.000	-23.946629	-18.989062
		VaD-like	-21.2949869*	.9435638	.000	-23.792847	-18.797127
	AD-like	Control-like	1.7023836	.9435638	.430	-.795476	4.200243
		MD-like	-19.7654617*	1.1522091	.000	-22.815660	-16.715263
		VaD-like	-19.5926032*	1.1580728	.000	-22.658324	-16.526882
	MD-like	Control-like	21.4678453*	.9363578	.000	18.989062	23.946629

		AD-like	19.7654617*	1.1522091	.000	16.715263	22.815660
		VaD-like	.1728584	1.1522091	1.000	-2.877340	3.223057
	VaD-like	Control-like	21.2949869*	.9435638	.000	18.797127	23.792847
		AD-like	19.5926032*	1.1580728	.000	16.526882	22.658324
		MD-like	-.1728584	1.1522091	1.000	-3.223057	2.877340

APPENDIX 7

Chapter 5: Group differences (between categories created using the 33rd percentile values of ypred score and WHM load) in age, average MMSE, WMH load, normalised hippocampal volume and ypred score in the portion of the BRC memory clinic cohort used in the chapter 5 study, as measured by ANOVA and Bonferroni's post-hoc tests. P < 0.05 is considered statistically significant.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
age	Between Groups	13645.235	3	4548.412	59.385	.000
	Within Groups	44806.592	585	76.592		
	Total	58451.827	588			
MMSE	Between Groups	1560.379	3	520.126	24.716	.000
	Within Groups	8922.883	424	21.045		
	Total	10483.262	427			
ypred - uncorrected	Between Groups	51.619	3	17.206	329.266	.000
	Within Groups	30.570	585	.052		
	Total	82.188	588			
normalise HC volume	Between Groups	.000	3	.000	130.016	.000
	Within Groups	.000	585	.000		
	Total	.000	588			
WMH load (mL)	Between Groups	57854.731	3	19284.910	297.868	.000
	Within Groups	37874.775	585	64.743		
	Total	95729.506	588			

Multiple Comparisons

Bonferroni

Dependent Variable	(I) group with ypred thirds	(J) group with ypred thirds	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
age	control-like	AD-like	-8.101*	.981	.000	-10.70	-5.51
		MD-like	-10.762*	1.083	.000	-13.63	-7.89
		VaD-like	-9.939*	.981	.000	-12.53	-7.34
	AD-like	control-like	8.101*	.981	.000	5.51	10.70
		MD-like	-2.661	1.261	.212	-6.00	.68
		VaD-like	-1.838	1.175	.710	-4.95	1.27
	MD-like	control-like	10.762*	1.083	.000	7.89	13.63
		AD-like	2.661	1.261	.212	-.68	6.00
		VaD-like	.823	1.261	1.000	-2.52	4.16
	VaD-like	control-like	9.939*	.981	.000	7.34	12.53
		AD-like	1.838	1.175	.710	-1.27	4.95
		MD-like	-.823	1.261	1.000	-4.16	2.52
MMSE	control-like	AD-like	3.017*	.594	.000	1.44	4.59
		MD-like	5.429*	.677	.000	3.63	7.22
		VaD-like	1.673*	.607	.037	.06	3.28

	AD-like	control-like	-3.017*	.594	.000	-4.59	-1.44
		MD-like	2.413*	.779	.013	.35	4.48
		VaD-like	-1.343	.719	.374	-3.25	.56
	MD-like	control-like	-5.429*	.677	.000	-7.22	-3.63
		AD-like	-2.413*	.779	.013	-4.48	-.35
		VaD-like	-3.756*	.789	.000	-5.85	-1.66
	VaD-like	control-like	-1.673*	.607	.037	-3.28	-.06
		AD-like	1.343	.719	.374	-.56	3.25
		MD-like	3.756*	.789	.000	1.66	5.85
ypred - uncorrected	control-like	AD-like	-.65504561900*	.02561409540	.000	-.7228528150	-.5872384230
		MD-like	-.67973798000*	.02828575700	.000	-.7546177620	-.6048581980
		VaD-like	-.21174174400*	.02561409540	.000	-.2795489400	-.1439345480
	AD-like	control-like	.65504561900*	.02561409540	.000	.5872384230	.7228528150
		MD-like	-.02469236090	.03294775850	1.000	-.1119136770	.0625289556
		VaD-like	.44330387500*	.03068472950	.000	.3620733870	.5245343630
	MD-like	control-like	.67973798000*	.02828575700	.000	.6048581980	.7546177620
		AD-like	.02469236090	.03294775850	1.000	-.0625289556	.1119136770
		VaD-like	.46799623600*	.03294775850	.000	.3807749190	.5552175520
	VaD-like	control-like	.21174174400*	.02561409540	.000	.1439345480	.2795489400

		AD-like	-.44330387500*	.03068472950	.000	-.5245343630	-.3620733870
		MD-like	-.46799623600*	.03294775850	.000	-.5552175520	-.3807749190
normalise HC volume	control-like	AD-like	.000561051738000*	.000037912776700	.000	.000460686722000	.000661416754000
		MD-like	.000675790902000*	.000041867244300	.000	.000564957378000	.000786624425000
		VaD-like	.000349298576000*	.000037912776700	.000	.000248933560000	.000449663592000
	AD-like	control-like	-.000561051738000*	.000037912776700	.000	-.000661416754000	-.000460686722000
		MD-like	.000114739163000	.000048767719300	.114	-.000014361718400	.000243840045000
		VaD-like	-.000211753162000*	.000045418090400	.000	-.000331986702000	-.000091519622200
	MD-like	control-like	-.000675790902000*	.000041867244300	.000	-.000786624425000	-.000564957378000
		AD-like	-.000114739163000	.000048767719300	.114	-.000243840045000	.000014361718400
		VaD-like	-.000326492326000*	.000048767719300	.000	-.000455593207000	-.000197391444000
	VaD-like	control-like	-.000349298576000*	.000037912776700	.000	-.000449663592000	-.000248933560000
		AD-like	.000211753162000*	.000045418090400	.000	.000091519622200	.000331986702000
		MD-like	.000326492326000*	.000048767719300	.000	.000197391444000	.000455593207000
WMH load (mL)	control-like	AD-like	-1.7444843	.9015864	.321	-4.131219	.642250
		MD-like	-20.4641154*	.9956257	.000	-23.099797	-17.828434

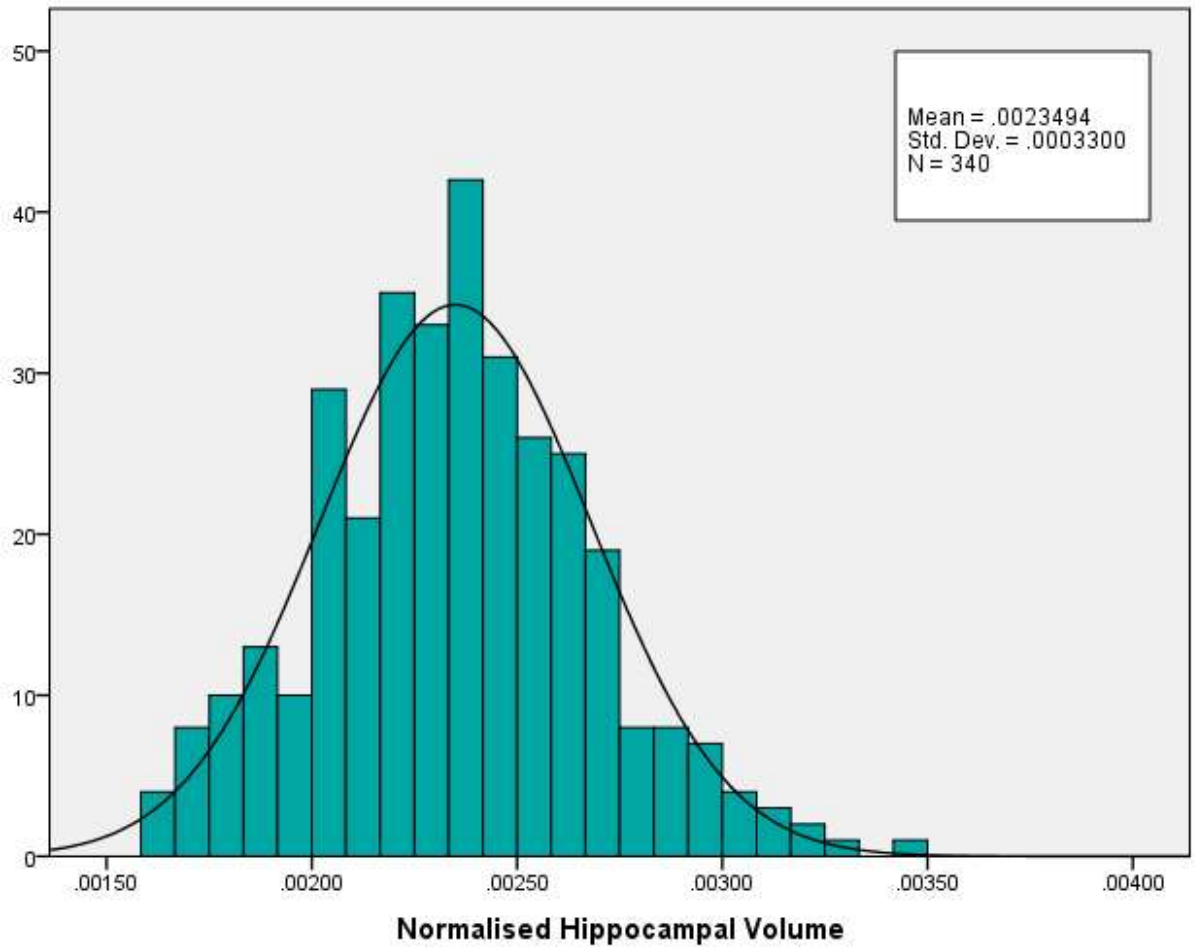
	VaD-like	-22.2134920*	.9015864	.000	-24.600226	-19.826758
AD-like	control-like	1.7444843	.9015864	.321	-.642250	4.131219
	MD-like	-18.7196311*	1.1597228	.000	-21.789720	-15.649542
	VaD-like	-20.4690077*	1.0800668	.000	-23.328226	-17.609789
MD-like	control-like	20.4641154*	.9956257	.000	17.828434	23.099797
	AD-like	18.7196311*	1.1597228	.000	15.649542	21.789720
	VaD-like	-1.7493766	1.1597228	.792	-4.819465	1.320712
VaD-like	control-like	22.2134920*	.9015864	.000	19.826758	24.600226
	AD-like	20.4690077*	1.0800668	.000	17.609789	23.328226
	MD-like	1.7493766	1.1597228	.792	-1.320712	4.819465

APPENDIX 8

Chapter 5: Calculation of mean (and standard deviation) normalised hippocampal volume of normal controls from the ADNI and AddNeuroMed Cohorts.

To compare normalised hippocampal volume values used for cut-offs, a set of 340 healthy controls from both the ADNI and AddNeuroMed datasets were analysed. Mean normalised hippocampal volume (right and left normalised hippocampi were averaged for each subject) and standard deviation were calculated. Statistics for normalised hippocampal volume and a histogram volumes with a normalised curve can be seen below.

N		340
Mean		0.002349
Median		0.002353
Std. Deviation		0.000330
Percentiles	*25*	0.002125
	50	0.002353
	75	0.002560



APPENDIX 9

Chapter 6: Ethical approval and approval of minor amendments for the Clinical Trial: *BrainMeasure: Automated Morphometry for Dementia Diagnosis*

NHS
Health Research Authority

NRES Committee London - City & East
Bristol Research Ethics Committee Centre
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 01173421386
Fax:01173420445

16 September 2014

Dr Sergi Costafreda Gonzalez
Clinical Lecturer
King's College, University of London
Institute of Psychiatry
16 De Crespigny Park
London
SE5 8AF

Dear Dr Costafreda Gonzalez

Study title:	**Automated brain morphometry for dementia diagnosis (BrainMeasure)**
REC reference:	**14/LO/0668**
IRAS project ID:	**132681**

Thank you for your letter of 02 September 2014, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair and Lead Reviewer.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Mr Rajat Khullar, nrescommittee.london-cityandeast@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the

study.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) - Trials and Human volunteers research study insurance		29 July 2013
GP/consultant information sheets or letters	1.1	20 August 2014
Non-validated questionnaire [SMME-standardised mini-mental state examination]		
Other [Patient questionnaire]	1	03 December 2013
Other [Clinician questionnaire]	1	03 December 2013
Other [Morphometric report example (Fig3)]	1	18 November 2013
Participant consent form [Participant consent form]	1.1	20 August 2014
Participant consent form [Carer consent form]	1.1	20 August 2014
Participant information sheet (PIS) [Participant information sheet]	1.1	20 August 2014
REC Application Form		02 April 2014
Referee's report or other scientific critique report [Scientific Review Ballard]		01 July 2014
Research protocol or project proposal	1	05 March 2014
Response to Request for Further Information		02 September 2014
Summary CV for Chief Investigator (CI)		18 November 2013
Summary, synopsis or diagram (flowchart) of protocol in non technical language		05 March 2014
Validated questionnaire [GAI-geriatric anxiety scale]		
Validated questionnaire [ACE-III-Addebrooke cognitive examination]		
Validated questionnaire [NPI- neuropsychiatric inventory]		
Validated questionnaire [GDS- geriatric depression scale]		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research

Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

14/LO/0668	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

pp Professor Arthur T Tucker
Chair

Email:nrescommittee.london-cityandeast@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Mr Keith Brennan,*
Ms Jenny Liebscher, South London And Maudsley NHS Foundation Trust

APPENDIX 10

Chapter 6: Average clinicians' rating of '*How likely are these patient's symptoms caused by AD?*' and '*How likely are these patient's symptoms caused by VaD?*' for each diagnostic category. Differences measured by one-way ANOVA and Bonferroni's post-hoc tests. One participant was excluded from this analysis (diagnosed with FTD) as they were the only person in that diagnostic category, and if included post-hoc analyses could not be conducted. P < 0.05 is considered statistically significant.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
How likely AD	Between Groups	90.173	5	18.035	22.703	.000
	Within Groups	66.727	84	.794		
	Total	156.900	89			
How likely VaD	Between Groups	42.735	5	8.547	9.239	.000
	Within Groups	77.712	84	.925		
	Total	120.447	89			

Multiple Comparisons

Bonferroni

Dependent Variable	(I) Final Diagnosis	(J) Final Diagnosis	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
How likely AD	No Diagnosis	Alzheimer's Disease	-2.0266*	.2690	.000	-2.839	-1.214
		Mild Cognitive Impairment	-.0588	.3104	1.000	-.997	.879
		Mixed Dementia	-1.8713*	.3104	.000	-2.809	-.933
		Vascular Dementia	-.3922	.5581	1.000	-2.079	1.294
		Other	.3697	.4003	1.000	-.840	1.579
	Alzheimer's Disease	No Diagnosis	2.0266*	.2690	.000	1.214	2.839
		Mild Cognitive Impairment	1.9677*	.2744	.000	1.139	2.797
		Mixed Dementia	.1552	.2744	1.000	-.674	.984
		Vascular Dementia	1.6344*	.5389	.048	.006	3.263
		Other	2.3963*	.3730	.000	1.269	3.523
		No Diagnosis	.0588	.3104	1.000	-.879	.997

	Mild Cognitive Impairment	Alzheimer's Disease	-1.9677*	.2744	.000	-2.797	-1.139
		Mixed Dementia	-1.8125*	.3151	.000	-2.765	-.860
		Vascular Dementia	-.3333	.5607	1.000	-2.028	1.361
		Other	.4286	.4039	1.000	-.792	1.649
	Mixed Dementia	No Diagnosis	1.8713*	.3104	.000	.933	2.809
		Alzheimer's Disease	-.1552	.2744	1.000	-.984	.674
		Mild Cognitive Impairment	1.8125*	.3151	.000	.860	2.765
		Vascular Dementia	1.4792	.5607	.149	-.215	3.173
		Other	2.2411*	.4039	.000	1.021	3.461
	Vascular Dementia	No Diagnosis	.3922	.5581	1.000	-1.294	2.079
		Alzheimer's Disease	-1.6344*	.5389	.048	-3.263	-.006
		Mild Cognitive Impairment	.3333	.5607	1.000	-1.361	2.028
		Mixed Dementia	-1.4792	.5607	.149	-3.173	.215
		Other	.7619	.6150	1.000	-1.096	2.620
	Other	No Diagnosis	-.3697	.4003	1.000	-1.579	.840
		Alzheimer's Disease	-2.3963*	.3730	.000	-3.523	-1.269
		Mild Cognitive Impairment	-.4286	.4039	1.000	-1.649	.792
		Mixed Dementia	-2.2411*	.4039	.000	-3.461	-1.021
		Vascular Dementia	-.7619	.6150	1.000	-2.620	1.096
How likely VaD	No Diagnosis	Alzheimer's Disease	.2372	.2903	1.000	-.640	1.114
		Mild Cognitive Impairment	-.1801	.3350	1.000	-1.192	.832
		Mixed Dementia	-1.3364*	.3350	.002	-2.349	-.324
		Vascular Dementia	-2.1176*	.6023	.011	-3.938	-.298
		Other	.5966	.4320	1.000	-.708	1.902
	Alzheimer's Disease	No Diagnosis	-.2372	.2903	1.000	-1.114	.640
		Mild Cognitive Impairment	-.4173	.2961	1.000	-1.312	.477
		Mixed Dementia	-1.5736*	.2961	.000	-2.468	-.679
		Vascular Dementia	-2.3548*	.5816	.002	-4.112	-.598

	Other	.3594	.4025	1.000	-.857	1.576
Mild Cognitive Impairment	No Diagnosis	.1801	.3350	1.000	-.832	1.192
	Alzheimer's Disease	.4173	.2961	1.000	-.477	1.312
	Mixed Dementia	-1.1563*	.3401	.015	-2.184	-.129
	Vascular Dementia	-1.9375*	.6051	.029	-3.766	-.109
	Other	.7768	.4359	1.000	-.540	2.094
Mixed Dementia	No Diagnosis	1.3364*	.3350	.002	.324	2.349
	Alzheimer's Disease	1.5736*	.2961	.000	.679	2.468
	Mild Cognitive Impairment	1.1563*	.3401	.015	.129	2.184
	Vascular Dementia	-.7813	.6051	1.000	-2.610	1.047
	Other	1.9330*	.4359	.000	.616	3.250
Vascular Dementia	No Diagnosis	2.1176*	.6023	.011	.298	3.938
	Alzheimer's Disease	2.3548*	.5816	.002	.598	4.112
	Mild Cognitive Impairment	1.9375*	.6051	.029	.109	3.766
	Mixed Dementia	.7813	.6051	1.000	-1.047	2.610
	Other	2.7143*	.6637	.001	.709	4.720
Other	No Diagnosis	-.5966	.4320	1.000	-1.902	.708
	Alzheimer's Disease	-.3594	.4025	1.000	-1.576	.857
	Mild Cognitive Impairment	-.7768	.4359	1.000	-2.094	.540
	Mixed Dementia	-1.9330*	.4359	.000	-3.250	-.616
	Vascular Dementia	-2.7143*	.6637	.001	-4.720	-.709